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AUSTRALASIAN ANNALS OF MEDICINE

VOLUME 3 FEBRUARY 1954 NUMBER 1

FEMALE PSEUDOHERMAPHRODITISM : RESPONSE TO CORTISONE THERAPY[1]

ROBERT VINES AND LORIMER DODS

From the Institute of Child Health and Royal Alexandra Hospital for Children, Sydney

Unseemly woman in a seeming man.
—" Romeo and Juliet ", Act III, Scene 3.

ADRENOCORTICAL HYPERPLASIA beginning during the early intra-uterine life of the female fœtus is responsible for the condition known as female pseudohermaphroditism, and the clinical features of this syndrome may be explained on the basis of quantitative and qualitative abnormalities of the hormones secreted by the hyperplastic adrenal cortices.

One of the earliest reports of female pseudohermaphroditism appeared in 1678, when Regnerus de Graaf of Leyden described and illustrated in detail the anatomical dissection of a female infant who presented all the classical features of this type of congenital abnormality, including gross enlargement of the clitoris, hypertrophy of the *labia majora* (Figure I), a normal uterus with normal Fallopian tubes and ovaries, and a vagina which joined the urethra to form what is now known as the " urogenital sinus ". About seventy years later James Parsons (1741) of London published a monograph entitled " A Mechanical and Critical Enquiry into the Nature of Hermaphrodites ", which makes no reference to any adrenal anomalies, but contains reports of several cases which might be accepted as classical examples of female pseudohermaphroditism, including the case history of a girl, aged thirteen years, with a grossly hypertrophied and " unperforated clitoris ", " a beard, hair on her body—voice, thorax, ischia and many other things like those of a man ". Apparently the association of these sexual abnormalities with adrenocortical hyperplasia was not recognized until the end of the nineteenth century, when Marchand (1891) described this syndrome. No published reports of the hypoadrenocorticism which may be associated with female pseudohermaphroditism and other forms of adrenocortical hyperplasia appeared until 1938, when Di Ruggiero and Jolly and later Wilkins *et alii* (1940) and Talbot *et alii* (1940) and their colleagues published studies of this aspect of the problem.

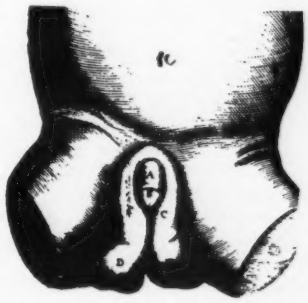

FIGURE I

Regnerus de Graaf's illustration of the external genitalia in female pseudohermaphroditism (1678).

INCIDENCE

Our clinical experience suggests that this condition is much more common than the literature suggests. During the past eight years one of us (L.D.) has examined at least eight children and one adult suffering from this syndrome, in addition to the six children who are the subjects of the present report. Dr. Douglas Reye, Director of Pathology, Royal Alexandra Hospital for Children, reports

[1] Received on November 6, 1953.

that during the same period six other infants suffering from female pseudohermaphroditism were examined in the post-mortem room of his department.

CLINICAL FEATURES

Excess of "androgens" secreted by the hyperplastic adrenal cortex during the intrauterine life of the affected infant is assumed to be responsible for the genital abnormalities

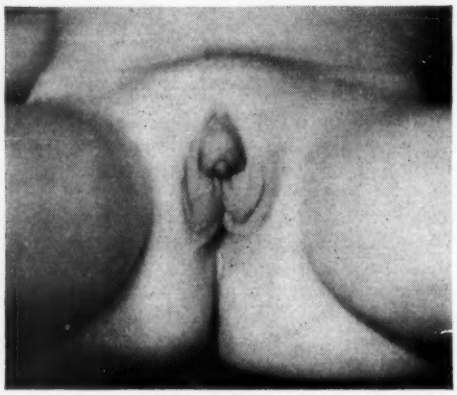

FIGURE II
External genitalia of female pseudohermaphrodite.

which are evident after birth. These abnormalities, which include gross enlargement of the clitoris and hypertrophy of the *labia majora*, the female homologue of the scrotum, may be responsible for the assumption that the infant is a male (Figure II) and as the "urethra" (in reality a urogenital sinus) usually opens at the base of the clitoris (Figure III), there is frequently a suggestion that this supposed male is suffering from hypospadias.

Apparently the excess of "androgens" produced by this form of prenatal adrenocortical hyperplasia usually disturbs the development of the female genital tract soon after the twelfth week of intrauterine life, when differentiation of the uterus, Fallopian tubes and ovaries is complete, but before the twentieth week or thereabouts when the anatomical relationships of the urethra and vagina are established; as a result of this disturbance, the vagina fails to develop normally and the urethra and vagina usually join to form a urogenital sinus (Figure IV). This communal sinus opens into a shallow vulval cleft, which may or may not be lined with mucous membrane. Apart from occasional abnormalities of the ovaries, the internal genitals are those of a normal female infant.

DIAGNOSIS

Careful inspection of the external genitals of an affected infant should be sufficient to prompt a tentative diagnosis of this condition. As adrenocortical hyperplasia may affect other siblings or other members of the family of an affected infant, a positive family history of this nature may be accepted as strong supporting evidence. A significant elevation of the urinary 17-ketosteroid level even during the early weeks of life, and, later, radiographic evidence of an advanced "osseous age", and the occasional presence of clinical features suggesting hypoadrenocorticism may confirm this diagnosis.

Infants and children suffering from adrenocortical hyperplasia may present clinical evidence of various degrees of hypoadrenocorticism as a result of the disturbance of their adrenocortical hormones. Infants suffering from female pseudohermaphroditism may present clinical evidence of this associated hypoadrenocorticism during the earliest weeks of their life, while others may pass through infancy without mishap and perhaps suffer

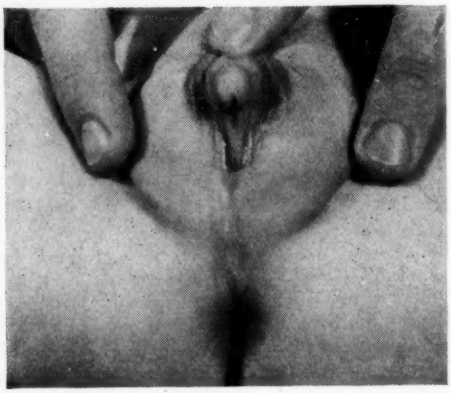

FIGURE III
External genitalia of female pseudohermaphrodite.

Addisonian-like crises during the later stages of childhood, as a result of an acute infection or a surgical procedure. Very rapid and unexplained weight loss or dehydration occurring during the early weeks of life, despite an adequate intake of fluid and calories, may be the first sign of hypoadrenocorticism. The real significance of these clinical signs may be masked by the vomiting and occasional diarrhœa which often characterize hypoadrenocorticism at this age, but the degree of dehydration is usually much greater than the gastro-intestinal symptoms would suggest.

NATURAL PROGRESS

During the first year of life further " androgenic " manifestations usually become obvious, and these include an increase in the size of the clitoris and a rapid increase in both " osseous age " and body growth. Pubic hair frequently appears before the age of three years, and axillary hair a little later ; acne, hypertrophy of body musculature and other male characteristics, including a prominent larynx and a deep voice, are often apparent before the age of six years, and the level of urinary 17-ketosteroids is grossly elevated.

The rapid statural growth and epiphyseal maturation which begin at a very early age continue for some years, and at the age of six or seven years the affected child may have a height and bone age of a normal girl of perhaps twelve or thirteen years. Later, premature closure of the epiphyses prevents further growth and may be responsible for producing a relatively short and stocky individual.

After the age of six or seven years all the distressing manifestations of " virilism " become progressively more apparent, and usually include an excess of hair on the body, limbs and face, and gross acne. As age advances through adolescence to adulthood, there is no obvious nipple or breast development, the menarche does not occur and both the body and face are essentially masculine in type ; this masculine appearance of the face is often intensified by the recession of the temporal hair line and the need for frequent shaving.

It would be difficult to overemphasize the sorrow and distress which such a condition brings to a family and the innumerable social and psychological problems associated with the girl's increasing " virilism ". The unfortunate girl frequently cuts herself off from social and athletic activities as she becomes increasingly aware of her obvious masculine features, and both she and her parents often become painfully aware of the " looks " and whispered comments of friends and strangers.

TREATMENT

One of us (L.D.) has passed through several phases in his attempts to deal with this distressing syndrome. Twenty years ago surgical removal of the clitoris seemed to be the obvious method of dealing with this problem, but this primitive mechanical approach failed to take into consideration the continuing and excessive secretion of " androgens " and the associated unrelenting and progressive " virilism " which finally mutilated the life of the unfortunate young woman. Partial adrenalectomy, with all its hazards, proved to be of no value, and even enormous doses of œstrogenic substances failed to mask the gross androgenic manifestations. With this knowledge and the realization that no " anti-androgenic " substance was available, it was felt that it was better to leave the hypertrophied clitoris *in situ*, and to allow the child to grow up as a " male ", exhibiting all those outward and visible signs of masculinity which belong to the adrenal hyperplasia syndrome.

During the past two years our whole attitude towards the treatment of these unfortunate patients has been dramatically changed as the result of the work of Wilkins and his colleagues (1950, 1951), who have shown that continued intramuscular administration of cortisone to children suffering from this condition causes a pronounced reduction in 17-ketosteroid and œstroid excretion, and that this reduction can be maintained.

Like all attempts at over-simplification of a complicated problem, the accompanying diagrams (Figure V) are almost certainly both

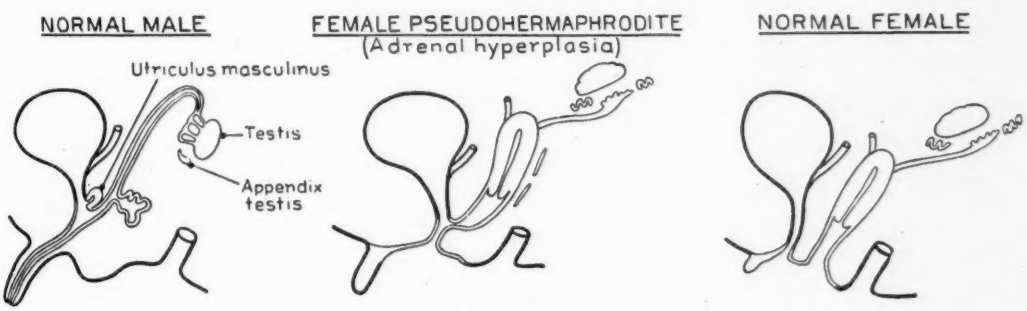

FIGURE IV

Persistent uro-genital sinus (from Wilkins, 1950).

inaccurate and incomplete; but they may help to illustrate some of the factors involved in the development and treatment of female pseudohermaphroditism. After several weeks of cortisone therapy corticotrophin administration no longer produces the usual pronounced rise in 17-ketosteroid excretion. This suggests that inhibition of corticotrophin formation by the

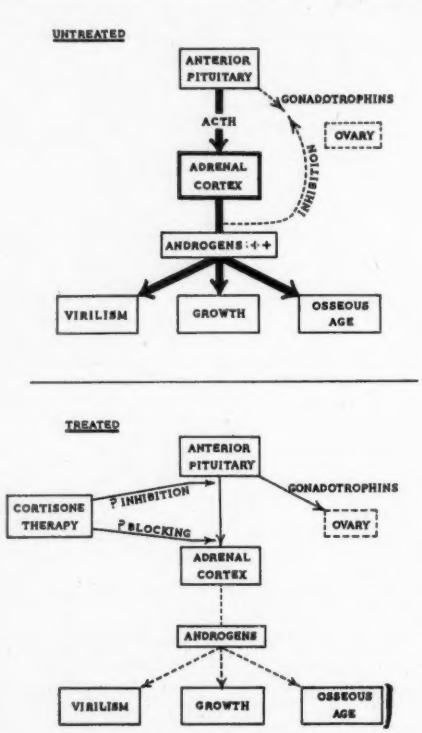

FIGURE V

Diagrammatic illustration of possible factors involved in the production and treatment of female pseudohermaphroditism.

administered cortisone is not the only mechanism which would explain its action, but that cortisone may, in some way, block the action of corticotrophin on the adrenal cortices. The rapid growth and skeletal maturation caused by the excessive hormonal output of the hyperplastic adrenal cortices cannot be maintained when cortisone is being given and reversion to normal rates occurs. Gonadotrophin production is suppressed by excessive adrenocortical activity; but cortisone, by diminishing this excessive activity, makes possible gonadotrophin production and consequent stimulation of the ovaries. With ovarian function restored and "androgen" production curtailed, "virilism" disappears and is replaced by feminization with breast development and menstruation.

Although cortisone suppresses adrenal "androgen" production, it would appear that abnormal production of other adrenocortical hormones continues, for, in dosage sufficient to suppress "androgen" production, cortisone causes little reduction in the symptoms of hypoadrenocorticism which are sometimes present. That these symptoms are the result of the production of abnormal hormones, or of the production of hormones in abnormal proportions, is suggested by the necessity which sometimes arises for giving doses of salt and deoxycortone larger than might be expected to be necessary if the adrenal cortices were absent.

REPORTS OF CASES

Since May, 1952, we have treated six female pseudohermaphrodites with cortisone.

CASE I.—D.L. was aged sixteen years when this form of treatment was commenced. There was no relevant family history, and her only sibling, an eleven year old boy, was well. The abnormality of her genitalia, an enlarged clitoris with "scrotal" labial folds separated by a mucosal cleft, was noted shortly after birth. She grew rapidly, but ceased growing at about the age of twelve years when 1·6 metres in height. Growth of the clitoris was observed in the first six months of life and continued. Pubic hair developed before the age of four years, and three years later gross hirsutism, acne and deepening of her voice were obvious. At the age of seven years laparotomy revealed small ovaries and a uterus; the clitoris was amputated at this time. This laparotomy was performed after preparation consisting of a diet of high salt and low potassium content and a saline infusion given after operation, as a previous attempt had been cut short by the child's collapse under anæsthesia. From the age of ten years she was treated intermittently with œstrogens, which produced the degree of breast development and the pigmentation of her nipples apparent in Figure VI. When she was aged twelve years, laparotomy performed by Mr. T. Y. Nelson revealed a right adrenal much larger than the left. The right adrenal was excised and found to be affected by adrenal hyperplasia with pronounced increase in the size of the reticular zone. No benefit was observed from this operation, and her hirsutism and failure to develop normal feminine characteristics became distressingly obvious. Prior to treatment with cortisone she was negativistic and frequently depressed, and presented a problem in management with which her unhappy parents had entirely failed to cope.

Two days before cortisone therapy was begun (25 milligrammes every eight hours by mouth), her urinary 17-ketosteroid excretion was 70 milligrammes in twenty-four hours. Figure VIII illustrates the rapid reduction in the urinary 17-ketosteroid excretion

to levels ranging from 9·4 to 13·2 milligrammes per twenty-four hours which was achieved under cortisone therapy. Wilkins *et alii* (1951) have suggested that at this age it is desirable to reduce the urinary 17-ketosteroid excretion to eight milligrammes per twenty-four hours, and in an endeavour to achieve this, larger doses of cortisone were given for some months without the desired effect. It appeared that the giving of larger doses of cortisone only resulted in higher 17-ketosteroid excretion levels, probably as a result of the excretion of a portion of the administered

FIGURE VI

Case I. Before treatment with cortisone.

FIGURE VII

Case I. After seventeen months' treatment with cortisone.

cortisone as 17-ketosteroids. The occurrence of a satisfactory clinical response seemed to support this probability.

After the administration of cortisone had been stopped for a period of fifteen days, high dosage (75 milligrammes every eight hours) was resumed and then reduced to 100 milligrammes daily within a month. Since this adjustment of dosage a satisfactory level of 17-ketosteroid excretion has been maintained.

The only side effects noted were moderate "facial mooning" and a gain in weight of 9·5 kilograms in seven months. At present there is no "facial mooning" and the girl is only 3·2 kilograms heavier than before commencing cortisone therapy. No elevation of blood pressure was observed.

Breast and nipple development became apparent within two months of the commencement of treatment. Breast tissue measured two centimetres in diameter before treatment, 4·5 to 7·5 centimetres in diameter after two months' treatment and 10·0 to 11·5 centimetres in diameter after fifteen months' treatment. The nipples and areolæ lost their former brown pigmentation. Acne diminished within two months of the commencement of therapy and has been absent for the past year. During the first year of treatment the skin became less oily and the complexion improved. These skin changes and the feminization of her bodily contours, which became apparent during the fifth month of treatment, have contributed to the dramatic feminization of her appearance which is apparent in Figure VII. Diminution in hirsuties was noted after some eight months' treatment and has become more and more obvious. This change affected mainly facial and limb hair, and she no longer needs to shave. Menstruation was scanty and occurred at irregular intervals at first, but was normal and regular after the thirteenth month of treatment. Along with these physical changes there has been a very pleasing change in personality. The patient is now a relatively happy, cooperative girl making a satisfactory adjustment to life. Her parents are, perhaps, even more strikingly happy and are no longer shame-faced.

CASE II.—K.F. was aged nine years and ten months when cortisone treatment was commenced. Three siblings were well and there was no relevant family history. She was registered as a boy at birth because of her large clitoris. This organ was amputated at the age of two years and its stump at the age of six years when laparotomy, performed by Mr. E. Goulston, revealed female internal genitalia of normal structure. Pubic hair appeared at the age of four years and axillary hair at the age of six years, when her voice became deep. Examination prior to treatment revealed a single cleft, lined with shiny, pink mucosa, between her hypertrophied and pigmented *labia majora*. No *labia minora* were obvious. She was unusually strong with pronounced muscular development, but her posture was poor. At the age of nine years her height, 1·52 metres, was approximately that of a girl of twelve years and her weight, 46·4 kilograms, about that of a girl aged thirteen and a half years, and her "osseous age" was assessed at sixteen to twenty years. She was intelligent, but sullen and intractable, and a source of great distress to her parents.

A urinary 17-ketosteroid estimation made not long before treatment was begun revealed a figure of 68 milligrammes in twenty-four hours. Cortisone, 25 milligrammes given orally every eight hours, caused a prompt reduction in this excretion (Figure IX). However, some later rise above the desired level of less than eight milligrammes per day occurred, and larger doses of cortisone failed to reduce the 17-ketosteroid excretion below this level until this dosage had been maintained for three months. Since then the isolated urinary 17-ketosteroid estimations which have been made have shown moderate fluctuations, but a number have been below eight milligrammes per day.

Transient "facial mooning" and a gain of 9·5 kilograms in weight occurred during the first seven months of treatment.

Failure to achieve maximal suppression of "androgen" production did not appear to delay clinical response. Breast development was apparent within two months of commencing therapy. No breast tissue could be felt before treatment began. After fifteen months of therapy, breast tissue was nine to 10 centimetres in diameter, and the nipples and areolæ were well developed and had lost their former brown pigmentation. Red striæ appeared on the hips in

association with an increase in hip measurement of 10 centimetres after four months' therapy, and had become paler after another ten months. Only slight acne had ever been present, but the girl's complexion improved considerably, the skin becoming less oily and a good colour appearing in her cheeks, while her slight facial and limb hirsuties diminished. The vulval mucosa became moist and bluish. Rather irregular, sometimes prolonged, menstrual periods occurred as indicated in Figure IX. There was no dysmenorrhœa. Her posture improved and she became happier and more sociable.

attained a " height age " of about ten years (1·4 metres) and a " weight age " of about eleven years (38 kilograms), and her " osseous age " was estimated at fourteen to sixteen years. There was no breast development, and the nipples and areolæ showed a moderate degree of brown pigmentation. The patient was a normally intelligent, happy girl with feminine interests. Her mother considered that her round-shouldered posture arose through an effort to appear less tall.

A urinary 17-ketosteroid excretion of 16 milligrammes in twenty-four hours was found at the age of

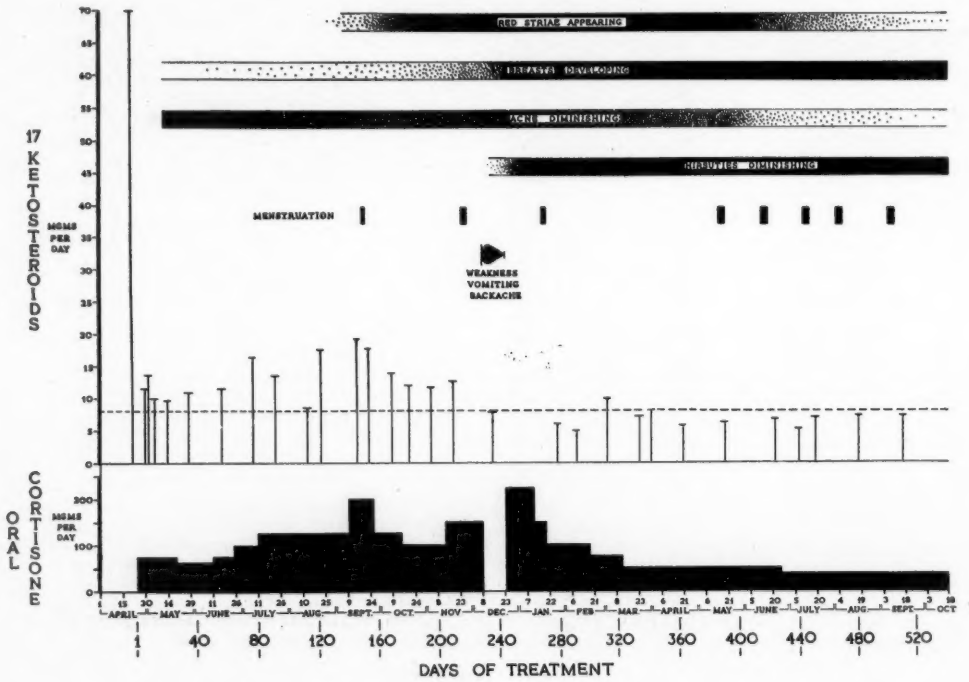

FIGURE VIII

Case I. Female pseudohermaphrodite, aged seventeen years. Details of response to cortisone therapy.

CASE III.—R.M., aged seven years, was an only child. A paternal aunt was said to be short, hairy, deep-voiced and masculine in manner and had remained single, but she experienced the menarche at the age of ten years and her subsequent menstrual history was said to be normal. The child's mother was short and had considerable hair growth about the nipples, while a maternal aunt, 1·5 metres in height, had borne two children (weighing between 1·8 and 2·3 kilograms) who lived for only a few hours. Abnormal growth of the child's clitoris was noted at the age of two years and before treatment commenced it was 2·5 centimetres long and 0·8 centimetre in diameter. Posterior to it lay a single mucosal cleft. Pubic hair appeared when she was three years old, and axillary hair a little later. Before treatment excessive hair growth had occurred on her heavily muscled lower limbs and about her lips. Rapid growth started when she was aged three years, and by the age of seven years she had four years, when laparotomy revealed female internal genitalia. Just prior to treatment her urinary 17-ketosteroid excretion was 24 milligrammes per day.

Cortisone, 25 milligrammes every eight hours, was given orally and caused a prompt reduction in urinary 17-ketosteroid excretion, but this reduction was not wholly maintained (Figure X). Subsequent increases and decreases in the dosage of cortisone failed to bring the urinary twenty-four hour 17-ketosteroid excretion to normal levels for her age, though it was brought to pubertal levels when 75 milligrammes of cortisone per day were being given. Slight " facial mooning " was the only side effect noted. The patient grew 4·5 centimetres in height and gained 4·5 kilograms in weight during the first five months of treatment. The earliest changes noted were cessation of masturbation and clitoral erections, and the occurrence of breast development; these changes occurred within two months of the commencement of treatment.

Breast tissue measured 3·8 centimetres in diameter after five months' treatment. What little acne was ever present disappeared. In the third month of treatment red striæ appeared on the buttocks; their appearance was associated with an increase of hip measurement of 6·3 centimetres. No change in personality was noted.

nine and a half years (1·36 metres) and a "weight age" of nine and a half years (31·3 kilograms) prior to treatment, and her "osseous age" was assessed at eleven to thirteen years. Her muscles were unusually well developed. When she was four and a half years old her voice became deep. She was a happy child, rather slow in learning and speaking poorly.

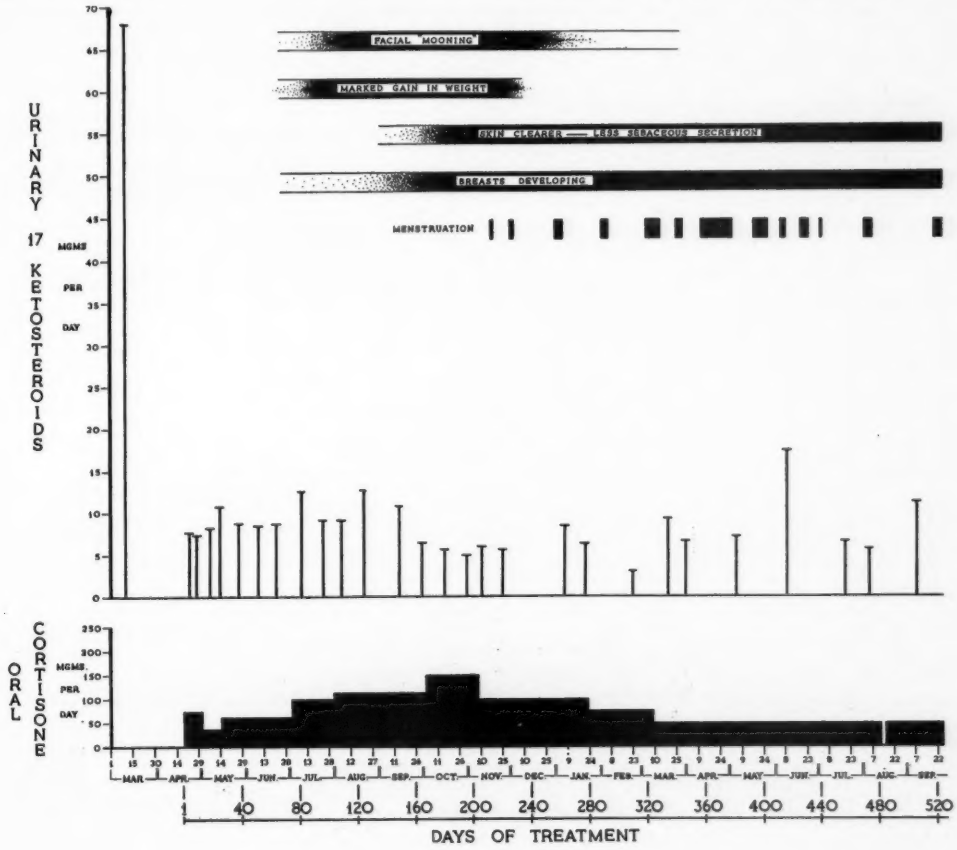

FIGURE IX

Case II. Female pseudohermaphrodite, aged nine years. Details of response to cortisone therapy.

CASE IV.—E.F. was aged five years and had two normal siblings. A paternal uncle is less than 1·5 metres in height and has one child. The patient's large clitoris, behind which was a single mucosal cleft, was noted at birth. Just prior to treatment the clitoris measured 3·8 centimetres in length and 1·25 centimetres in diameter. Pubic hair appeared when she was aged two years, and at this time laparotomy, performed by Mr. E. Goulston, revealed normal female internal genitalia and a right adrenal gland which was rather larger than normal. A pulse rate of 200 per minute at the conclusion of this operation caused concern, but her condition soon improved without specific treatment. Rapid growth took place after this time and she had attained a "height age" of

Prior to the commencement of cortisone therapy her twenty-four-hour urinary 17-ketosteroid excretion was 29 milligrammes. Prompt reduction in the levels was obtained by giving cortisone orally, but the levels were not reduced to those usual for her age, but rather to those usual at puberty. It would appear that a sustained, maximal reduction in 17-ketosteroid excretion was not achieved after five months of treatment. Despite this, signs of feminization were apparent; her severe acne diminished and breast development commenced within two months of the commencement of therapy. After three months' treatment no acne remained, her breast tissue was 2·5 centimetres in diameter and there had been no change in height or weight. No change in personality was observed.

CASE V.—S.S. was the only child of healthy parents. There was no relevant family history. Delivery had been normal, and the birth weight was 3·1 kilograms. Vomiting, sometimes projectile, accompanied at times by the passage of frequent motions, started a few days after birth. Despite these symptoms the serum sodium content was 139 milliequivalents per litre, the serum potassium content was 6·2 milliequivalents per litre and the serum chloride content was 105 milliequivalents per litre at the age of three weeks. Apart from emaciation she showed no abnormalities prior to this excretion was obtained; but only infrequently, despite alterations in the dosage of cortisone, did it fall within the range of 1·4 to 1·7 milligrammes per day, which Wilkins *et alii* (1951) have suggested is a desirable amount. In the seventh month of treatment cortisone was given intramuscularly for two weeks, and since that time satisfactory reduction in urinary 17-ketosteroid excretion has been maintained. During the periods when the larger doses of cortisone were being given the infant was hyperactive and inclined to be irritable and developed transient " facial mooning ".

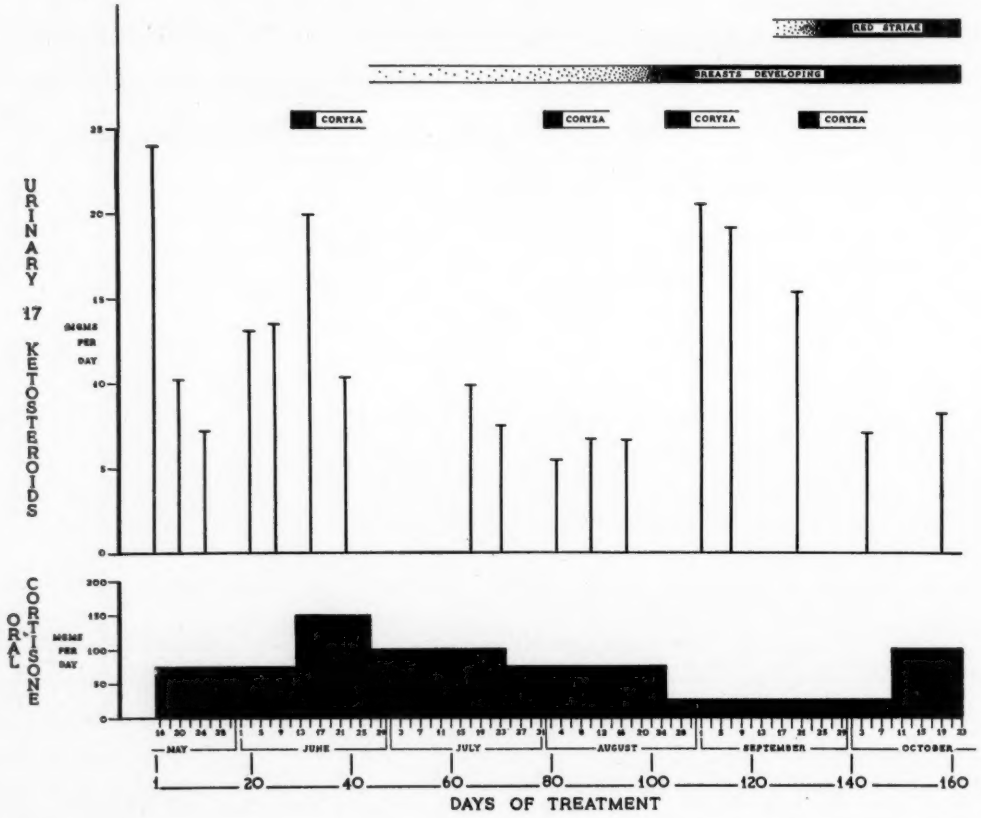

FIGURE X

Case III. Female pseudohermaphrodite, aged seven years. Details of response to cortisone therapy.

treatment other than the presence of a greatly enlarged clitoris, behind which were " scrotal " labial folds and a single mucosal cleft. Her " osesous age " was within normal limits.

Treatment was commenced at the age of ten weeks by the oral administration of five milligrammes of cortisone at eight-hourly intervals. She not only regained her birth weight but continued to gain in weight, though rather slowly, for vomiting persisted till she was six months old. A twenty-four hour urinary 17-ketosteroid estimation prior to treatment gave a figure of 2·3 milligrammes. Some reduction of this infant had a number of respiratory infections which were associated with vomiting, prostration, weight loss and dehydration on several occasions, and which twice necessitated her admission to hospital for intravenous therapy. On the occasion of her last admission to hospital abnormalities of serum electrolytes suggesting hypoadrenocorticism—namely, a serum sodium content of 117 milliequivalents per litre and a serum potassium content of 6·2 milliequivalents per litre—were found. After that time two grammes of added salt were given daily, and this amount was increased to four to six grammes when she appeared

off colour or had an obvious infection. With this alteration she was able to weather pertussis and another severe respiratory infection without requiring admission to hospital. After seventeen months of treatment she was a rather short, plump infant of apparently normal intelligence with a relatively smaller clitoris hidden between labial folds which were no longer pigmented or "scrotal" in character. Her "osseous age" remained within normal limits, and no unusual hair growth occurred.

CASE VI.—L.R. was the third child of healthy parents. The other two children had presented similar genital abnormalities at birth, and both had died at the age of one month. Adrenocortical hyperplasia was found when post-mortem examination was performed on the second of these infants. The patient had a clitoris 1·7 centimetres in length and 0·8 centimetre in diameter. Posterior to this were pigmented, "scrotal" *labia majora*. Unlike the long cleft found in the other five cases of this series, the opening of the uro-genital sinus in this infant consisted of a small, anteriorly directed orifice, two millimetres wide, situated just below the base of the clitoris. The "osseous age" was within normal limits. For several days after birth the infant's condition was good, but weight loss continued despite a satisfactory food intake and the absence of vomiting and diarrhœa, so that at the age of nine days the infant was dehydrated and weak and showed severe peripheral cyanosis. Added salt, either in the feedings or given as subcutaneous saline infusions, and later cortisone given intramuscularly in addition, failed to produce sustained improvement, either in the clinical condition or in the serum electrolyte contents (Figure XV). The urinary 17-ketosteroid excretion rose higher than its already increased pretreatment levels when 25 milligrammes of cortisone were being given daily, but subsided to normal levels when the dose was decreased.

Daily intramuscular injections of deoxycortone acetate were commenced, and distinct clinical improvement, better colour and gain in weight, despite continuing abnormalities of serum electrolytes, followed increase of the dose of deoxycortone acetate to seven milligrammes daily. On two occasions cyanosis and collapse occurred during feedings, and chest radiographs taken after these episodes revealed areas of pulmonary collapse and consolidation.[1]

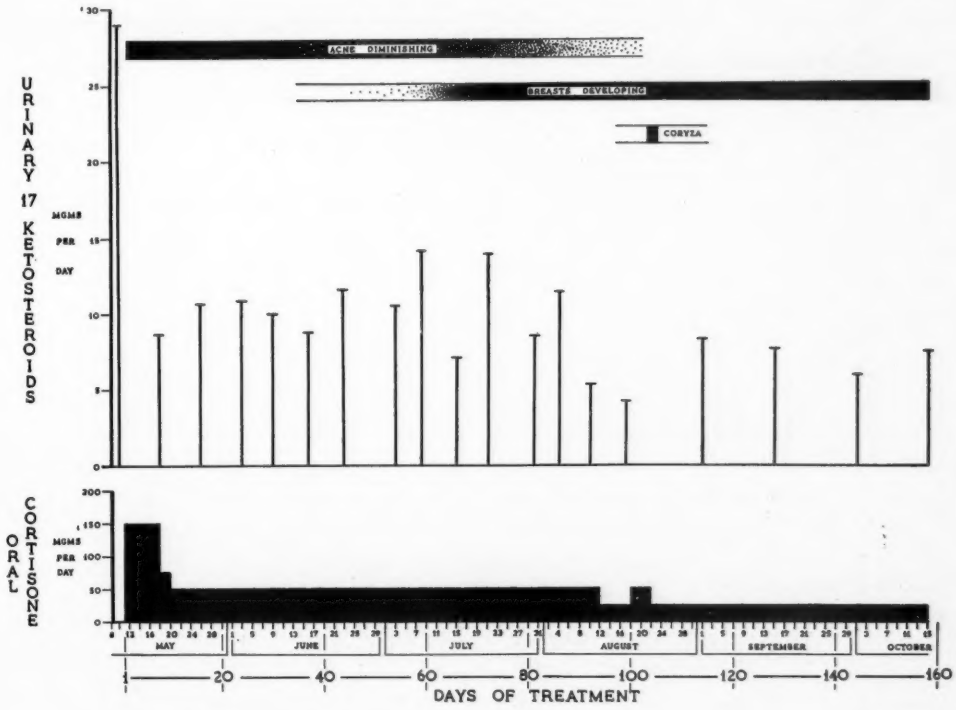

FIGURE XI

Case IV. Female pseudohermaphrodite, aged five years. Details of response to cortisone therapy.

[1] A satisfactory clinical condition and normal values for serum electrolytes were finally achieved by giving the heroic dose of 18 milligrammes of deoxycortone intramuscularly daily, together with four grammes of added salt and one gramme of sodium bicarbonate daily.

DISCUSSION

The first changes to become apparent with cortisone therapy are breast development and diminution in acne. These changes were noted by the end of the second month of treatment in the first four cases of this series. Not only did acne disappear, but a decided improvement in the girls' complexions occurred, the skin becoming less oily and softer, and fresh

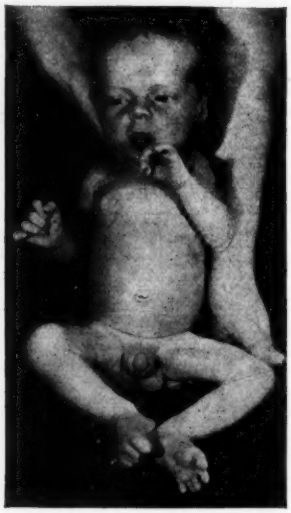

FIGURE XII

Case V. Before treatment with cortisone.

colour appearing in the cheeks. Breast development associated with normal nipple and areolar development occurred in both the seven year old and the five year old girls. That breast development should occur in such young children may be due to the priming effect of the excessive hormones produced by the adrenal cortices, and the advanced " osseous ages " of these children may be accepted as evidence that their bodies were prepared for pubertal changes. The pigmentation of nipples and areolæ present in the first three cases of this series faded within several months of the commencement of cortisone therapy.

Purplish striæ appeared on the hips of these three children within three to five months of the commencement of therapy. In each case the appearance of striæ was associated with feminization of contours and increased hip measurement. Waist measurements remained the same, or diminished, despite weight increases.

Diminution in the growth of beard and limb hair was obvious in Cases I and II and is still progressing ; this change appears to be mainly one of replacement of dark, coarse hair by fine, fairer hair. No alteration in the growth of sexual hair was noted.

The menstruation which occurred in Cases I and II was not associated with dysmenorrhœa, but was prolonged and irregular in Case II. That some imbalance of pituitary-ovarian function should occur in these girls would not be surprising and might explain this irregularity.

Wilkins and his associates (1952) have recorded basal temperature changes suggesting that ovulation occurs in these treated girls. As congenital adrenocortical hyperplasia appears to be inherited along Mendelian recessive lines, the advisability of these girls' bearing children may be questioned.

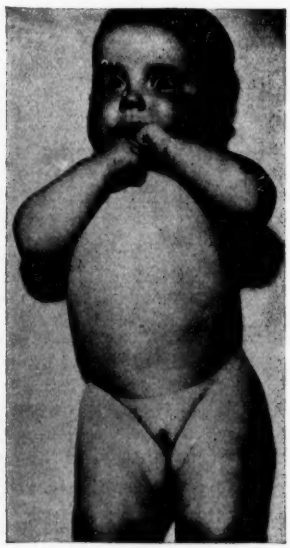

FIGURE XIII

Case V. After seven months' treatment with cortisone.

The clitoris is now relatively smaller in Case V, but no change in this organ has been apparent in the other three children (Cases III, IV and VI), except a diminution or absence of erections, and in Case III cessation of masturbation. The vulval mucosa in Cases I and II has changed from its former pink and shiny state to become more blue and moist.

Although the deep voices of three of the children (Cases I, II and IV), remained unchanged, they ceased to cause concern.

One of the happiest results of cortisone therapy in this series was the remarkable improvement in personality seen in the two oldest children (Cases I and II). Their sullen negativism and depression went and their round-shouldered, head-low posture improved, as if they could now bear to face the world. These changes are happily reflected in their parents. The younger the child, the less dramatic are the changes produced by cortisone therapy, so that it seems likely that the younger ones of this series and their parents will never realize the distress they have been spared.

Too little time has elapsed to allow any general statement to be made in regard to the effect of cortisone therapy on growth. In Case V growth occurred along normal lines, but at a moderately reduced rate, which may be due to the use of rather large doses of cortisone for a period and to the severity of this child's reactions to minor infections.

The degree of associated hypoadrenocorticism present was very variable. In Cases I and III alarming reactions occurred during operations, and these reactions may well have been due to the presence of some degree of hypoadrenocorticism. It would seem wise to try to prevent these occurrences in all those with adrenocortical hyperplasia by administering electrolytes and hormones, appropriate for the control of hypoadrenocorticism, before and after operations. A moderate degree of hypoadrenocorticism was present in Case V; but an increased salt intake was sufficient to prevent minor infections causing grave prostration. The disorder of electrolyte metabolism in Case VI was very severe, necessitating the giving of salt and deoxycortone in quantities which would prove lethal to a normal infant.

Larger doses of cortisone were given in this series than in others reported; but side-effects were limited to the development of "facial

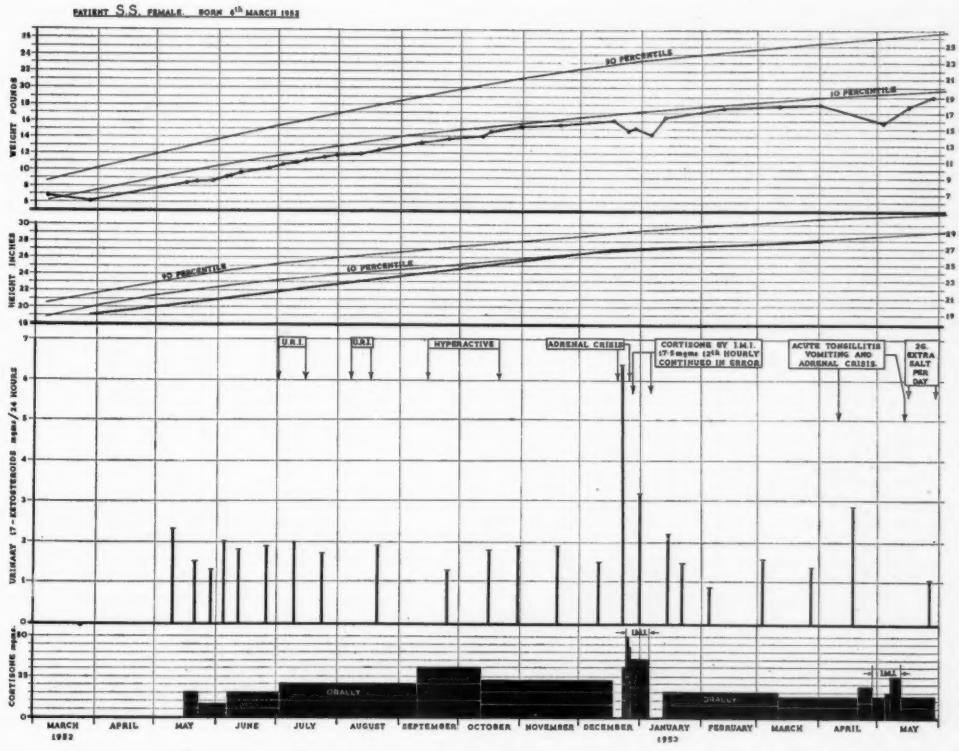

FIGURE XIV

Case V. Infant female pseudohermaphrodite; response to cortisone therapy.

mooning " and moderate weight gain in Cases I and II, a slight and transient elevation of blood pressure in Case II, and hyperactivity and " facial mooning " in Case V. None of these signs persisted when the children were receiving the smaller maintenance doses of cortisone.

The less reliable response of the adrenal cortices to cortisone given orally, the greater proportion of cortisone excreted as 17-ketosteroids when it is given by mouth, and the Despite this the accompanying graphs suggest that, after initiation of therapy with cortisone given by mouth, maximal suppression of 17-ketosteroid excretion may be obtained only after a period of months of relatively high dosage. Although Wilkins and his associates (1951) have recommended that the 17-ketosteroid excretion should be depressed to eight milligrammes or less per day in children of pubertal age and to 1·4 to 1·7 milligrammes

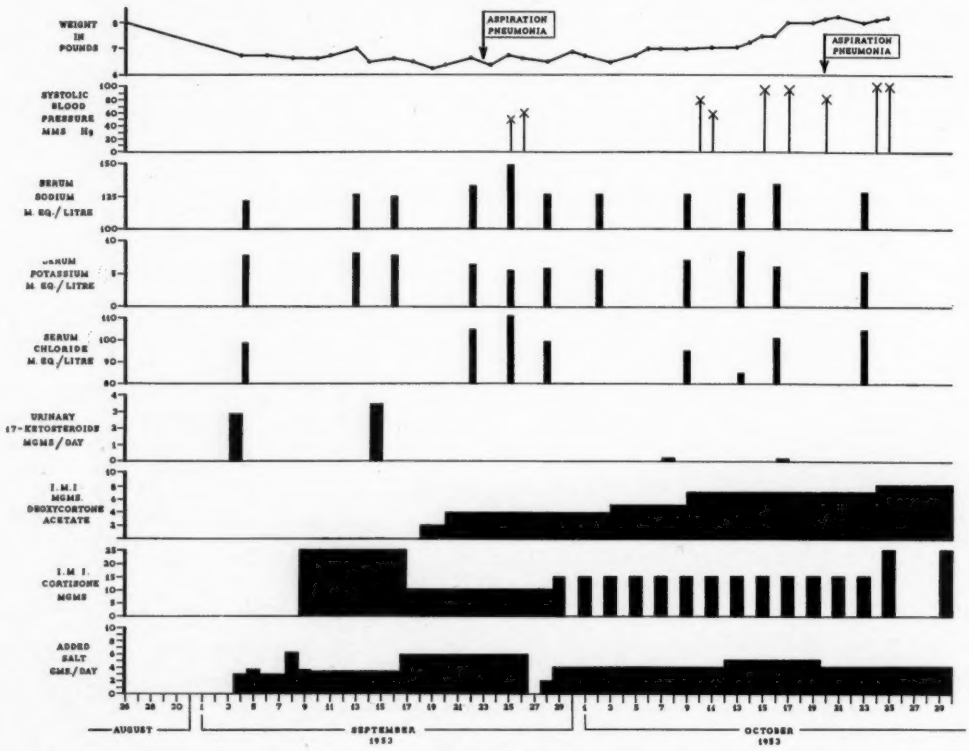

FIGURE XV

Case VI. Female pseudohermaphroditism complicated by severe disturbance of electrolyte metabolism; observations and treatment. Baby born August 26, 1953.

method used in estimating 17-ketosteroid excretion (Callow, Callow and Emmens, 1938) may have been responsible for the fact that in this series of children the 17-ketosteroid excretion was not reduced to such low levels as in other cases reported. It is realized that the significance of isolated urinary 17-ketosteroid estimations is difficult to assess in view of the varying contributions to their levels made by the administered cortisone, and of the rise in levels caused by infections and other " stresses ". per day in infants, our limited observations suggest that a satisfactory clinical response may be obtained with a lesser degree of depression of 17-ketosteroid excretion.

Our experience with the first five cases of this series has shown that the oral administration of cortisone can be a practical way of initiating and maintaining therapy for congenital adrenocortical hyperplasia. However, there are several reasons for suggesting that initiation of treatment should be by the parenteral route.

Depression of 17-ketosteroid excretion is more reliably achieved by giving cortisone intramuscularly, and smaller doses are required. Obviously, if vomiting associated with disturbed electrolyte metabolism is present, parenteral administration is essential.

Although the most important criterion of adequate treatment appears to be the clinical response, serial estimations of urinary 17-ketosteroid excretion and of "osseous age" are helpful for controlling dosage.

How long administration of cortisone will continue to be necessary, or even whether it will continue to be effective, are questions that remain unanswered.

SUMMARY

Cortisone has been used to treat six children suffering from female pseudohermaphroditism due to congenital adrenocortical hyperplasia.

Oral administration of cortisone has been used for both initiation and maintenance of treatment in five of these children with satisfactory results, but it is suggested that the parenteral route is preferable during the initial stage of treatment.

Depression of 17-ketosteroid excretion, and loss of "virilism" or failure of "virilism" to appear, have been observed in each case.

Whatever course this therapy follows in the future, it is certain that it has already brought much happiness to a most distressed group of children and parents.

ACKNOWLEDGEMENTS

The authors are indebted to Dr. A. K. Boultt, Dr. D. G. Hamilton, Dr. C. W. G. Lee and Dr. A. S. B. Studdy for referring patients, and to Dr. A. S. Brett for assistance with Case II. Our thanks are also due to Miss E. A. Stobo for estimating 17-ketosteroid and electrolyte levels.

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THE SPATIAL VECTORELECTROCARDIOGRAM IN RIGHT VENTRICULAR HYPERTROPHY[1]

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RECENTLY we presented the vectorelectrocardiographic patterns found in left ventricular hypertrophy due to established hypertension (Gardiner and Lowe, 1953). In the present paper an analysis is made of the vectorelectrocardiogram (VCG) in right ventricular hypertrophy as it occurs in congenital heart disease, mitral stenosis and some other conditions, including pulmonary heart disease.

CLINICAL MATERIAL AND METHODS

The series comprises 68 patients attending the Alfred Hospital who were suffering from conditions which can be presumed to lead to hypertrophy of the right ventricle and to have little or no effect on the left ventricle. The cases fall into three groups. The first group contains 22 cases of congenital heart disease, including six cases of simple pulmonary stenosis, ten of Fallot's tetralogy, three of the Eisenmenger syndrome with pulmonary hypertension, and three of atrial septal defect. The diagnosis was confirmed in 13 cases at cardiac catheterization and in four at operation. The ages of this group ranged from four to thirty-five years with a mean of eighteen years.

The second group consists of 36 patients suffering from mitral stenosis uncomplicated by systemic hypertension, aortic valve disease, or mitral incompetence of more than slight degree. The severity of the mitral stenosis varied from mild to severe. Twenty-eight patients had sufficient disability to be treated by mitral valvotomy, at which the diagnosis was proved in all; the surgeon found the stenosis to be severe in 22 and moderate in six. Two of the severely affected subjects came to necropsy, at which the presence of right and the absence of left ventricular hypertrophy were confirmed. The ages of this group ranged from seventeen to fifty-three years with a mean of thirty-eight years.

In the third group are ten miscellaneous cases, comprising seven of pulmonary heart disease, two of primary pulmonary hypertension, one of which was proven at necropsy (Clarke and Tait Smith, 1953), and one case of rheumatic mitral and tricuspid valve disease in a child, who presented necropsy evidence of right ventricular hypertrophy. The ages of this group ranged from eight to fifty-nine years with a mean of thirty-seven years.

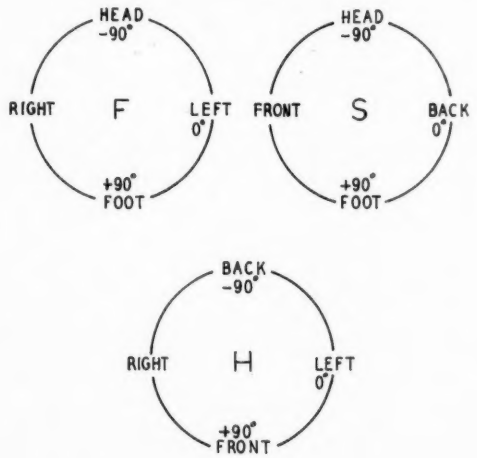

FIGURE I

Diagram to show the orientation of the V.C.G. loops in all illustrations.

The VCG's were recorded by the methods employed previously (Lowe and Goble, 1952). Frontal, sagittal and horizontal projections of the spatial loop were photographed in pairs simultaneously. The orientation of the projections is shown in Figure I. Low amplification tracings recorded the general contour of the whole spatial loop; high-amplification tracings were used to clarify events about the origin.

[1] Received on September 11, 1953.

[2] Part of this work was done during the tenure of the Victor Y. and Margaret Kimpton Research Scholarship, Alfred Hospital, Melbourne.

[3] Part of the expenses of this investigation have been defrayed by a grant from the National Health and Medical Research Council.

RESULTS

Analysis of the Auricular (P) Complex

The auricular complex (*P* loop) was absent in 16 cases, owing in 15 to auricular fibrillation and in one to auricular flutter. Of the remaining 52 cases, in 21 there were definite abnormalities of the *P* loop: two were in the congenital group, 12 in the mitral group and seven among the miscellaneous cases.

The normal *P* loop is directed downwards and somewhat to the left; it is well seen in the frontal and sagittal planes, but not as a rule in the horizontal. In the frontal plane it is round or elongated and often bifid at the lower end.

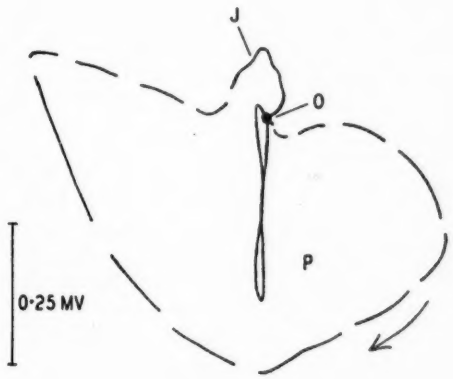

FIGURE II

Traced drawing of frontal projection of VCG in a case of pulmonary heart disease, showing an abnormally long *P* loop. Time markers in all VCG's are 0·005 second apart.

Variations in this pattern considered to be abnormal consisted of one or more of the following features: (i) increased amplitude; (ii) change of contour to either a bifid or a triangular loop; (iii) change of axis.

There was great variety in the contour of the abnormal loops; the most consistent pattern was the long, narrow, vertical loop seen in six of the seven cases of pulmonary heart disease (Figure II).

Analysis of the Ventricular (QRST) Complex

Duration of the QRS Loop.—The normal *QRS* duration is from 0·06 second to an upper limit of 0·10 second. In this series the *QRS* duration was prolonged to beyond 0·10 second in three cases of congenital heart disease. The duration was 0·10 second in a further two cases, one of congenital heart disease, and one of pulmonary heart disease. In all these cases the slowing occurred in the terminal third of the loop, and the slow segment was directed in towards the junction (*J*) of the *QRS* and *T* portions of the *QRST* complex from the right and slightly forwards. This also occurs characteristically in the *QRS* loop of right bundle branch block.

Direction of Inscription of the QRS Loop.—In the normal VCG the frontal loop may be written either clockwise or anticlockwise, but the sagittal and horizontal loops are written anticlockwise. The direction of inscription in the sagittal projection was abnormal in 14 cases of congenital heart disease, in ten of mitral stenosis and in seven miscellaneous cases.

TABLE I

Direction of Inscription of QRS *Loop*

Group	Sagittal		Horizontal	
	Normal	Abnormal	Normal	Abnormal
Congenital heart disease	8	14	1	21
Mitral stenosis ..	26	10	22	14
Miscellaneous ..	3	7	1	9

In the horizontal projection it was abnormal in 21 cases of congenital heart disease, in 14 of mitral stenosis and in nine miscellaneous cases (Table I). These constitute the majority of subjects with *QRS* loops considered to be abnormal.

Direction of the Long Axis of the QRS Loop.—Figure III is a histogram of the direction of the long axis of the *QRS* loop as recorded in each of the three projections in the three groups of cases. Beneath the histogram are given the limits and the median of the directions found in the normal series of 68 cases reported previously. It will be seen that there is a "shift to the right" of the long axis of the *QRS* loop in the frontal projection and a shift forwards in the sagittal projection. In the horizontal projection a considerable number of axes are outside the normal limits and are strongly rotated to the right. Abnormality in axis direction is thus most commonly and clearly seen in the horizontal projection. This contrasts with left ventricular hypertrophy, in which the sagittal projection is the most informative in this regard.

Contour of the QRS Loop.—*QRS* loops which did not conform with the criteria set out

in a previous paper (Lowe and Goble, 1952) were considered to be abnormal. Such loops in this series showed as a rule a distorted contour. When this was combined with abnormalities in the direction of the long axis and general orientation of the loop, in the regularity and rate of its inscription, and sometimes in its duration, certain characteristic patterns were produced. The majority of abnormal loops had one or both of the following features (Table II):

1. A distortion of the loop, in which, after a normal initial crochet and first part or perhaps whole of the centrifugal limb, the path of the loop before returning to the origin (*O*) was directed strongly to the right, often upwards and usually in front of *O*. Thus the general direction of distortion was to the right, perhaps upwards, and somewhat forwards. It produced very characteristically a clockwise horizontal loop (Figures IV and V).

2. A slowing in the rate of inscription of the loop as it travels in from the right to *J* (Figure VI). The slowing was of varying degree; in the cases in which it was pronounced, the total loop duration was prolonged. It was usually combined with some degree of distortion, with deviation of the loop to the right of *O* before the slowing occurred. In the majority of cases the rotation in the horizontal plane was clockwise, although in a few the distortion was less pronounced and this abnormality was absent (Figure VI). In no case could the slowing be described as part of a secondary loop written after the primary loop had returned nearly to the origin, as may be found in cases of right bundle branch block without evidence of right ventricular hypertrophy. Whether the loop slowing does in fact represent a complete or incomplete right bundle branch block is uncertain; it would appear to reflect late activation of a certain mass of muscle on the right side, but the reason for this has not been established.

In the cases of congenital heart disease, the pattern seen was usually a strong distortion to the right; this occurred in 20 of the 22 cases. In eight of these there was a terminal slower portion coming in from the right; in two this was pronounced and the total duration was prolonged.

One subject showed a more bizarre picture; the loop, after a normal first half of the centrifugal limb, travelled upwards high over *O* to the right, ending in a very slow "run-in" with prolonged total duration. One subject showed an abnormal (figure of eight) horizontal loop only.

In the group with mitral stenosis, 12 subjects showed a right-sided distortion pattern; two of these subjects also showed terminal slowing. Two further subjects showed a distortion which was probably abnormal but less pronounced, the horizontal loop remaining anticlockwise in inscription. Five subjects showed a slowed terminal "run-in" from the right side to *J* without definite loop distortion. Two subjects showed a bizarre pattern considered abnormal,

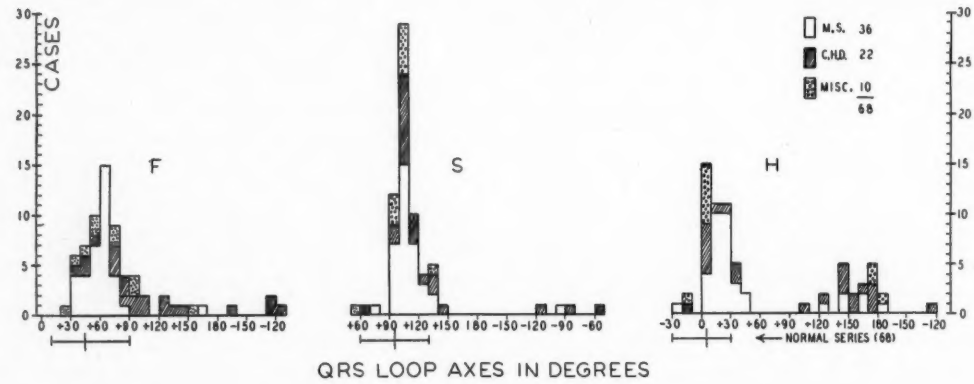

FIGURE III

Histograms showing the frequency distribution of the *QRS* axis angles in the frontal (F), sagittal (S) and horizontal (H) planes in the three groups. Beneath each histogram are given the range and median of the axis angles in a series of normal subjects. M.S., mitral stenosis; C.H.D., congenital heart disease; Misc., miscellaneous group.

but not conforming to the general types mentioned. One subject showed an abnormal (figure of eight) horizontal loop only. The remaining 14 subjects had *QRS* loops considered to be normal.

TABLE II
QRS *Loop Contour*

Type of *QRS* Loop	Congenital Heart Disease	Mitral Stenosis	Miscellaneous
Normal	—	14	—
Abnormal	22	22	10
Initial crochet ..	4	6	—
Distortion of loop to right	20	12	9
Slowed terminal segment	9	7	4
Increased duration	3	—	—

In the miscellaneous group nine subjects had a loop distorted to the right, three of whom also had a terminal slowed segment. One subject had a slowed " run-in " to *J* from the right, without other evidence of distortion.

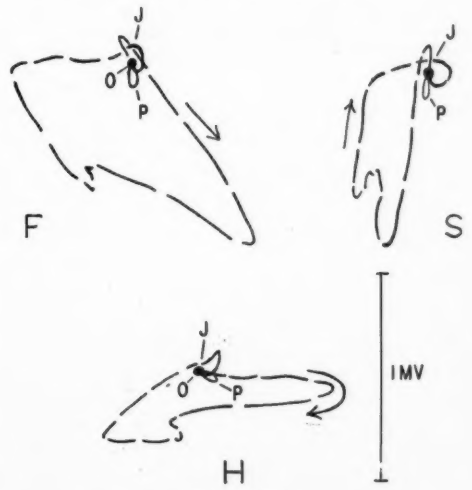

FIGURE IV

Traced drawings of VCG in a case of primary pulmonary hypertension, showing the general distortion of the loop to the right and forwards with some terminal slowing of inscription. A J-shift is present.

With regard to the individual parts of the *QRS* loop, the initial crochet was abnormal in ten cases—four of congenital heart disease and six of mitral stenosis ; the centrifugal limb was abnormal in 12 cases of congenital heart disease, nine of mitral stenosis and six miscellaneous cases ; the centripetal limb was abnormal in 21 cases of congenital heart disease, in 18 of mitral stenosis and in nine miscellaneous cases ; and the terminal segment was abnormal in 18 cases of congenital heart disease, in 22 of mitral stenosis and in 10 miscellaneous cases.

Displacement of the QRS-T Junction.— In normal subjects *J*, the junction of the *QRS* loop with the remainder of the ventricular complex, coincides almost exactly with *O*, the origin of the loop ; a " shift " of *J* of more than mild degree in abnormal.

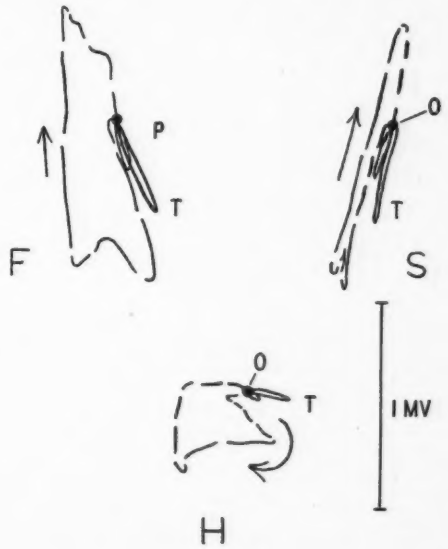

FIGURE V

Traced drawings of VCG in a case of Fallot's tetralogy, showing the general distortion of the loop to be upwards as well as to the right and forwards.

In this series there was a *J*-shift in seven cases of congenital heart disease, in 16 of mitral stenosis, and in five in the miscellaneous group.

The direction of the shift in the three groups is shown in Table III. It will be seen that in the majority of cases the shift was upwards, backwards and usually to the right.

In contrast, in left ventricular hypertrophy (Gardiner and Lowe, 1953), it was found that the *J*-shift was almost always to the right and never to the left, often upwards and often forwards, but rarely back.

Only three subjects with a *J*-shift had a normal *QRS* loop ; one of them had in addition an increased *QRS-T* angle. As all were taking full doses of digitalis, it is likely that the *J*-shift was a digitalis effect in these cases.

However a *J*-shift may occur independently of digitalis administration. For instance, it occurred in six of the 21 subjects of congenital heart disease not taking digitalis (Figures VII and VIIA).

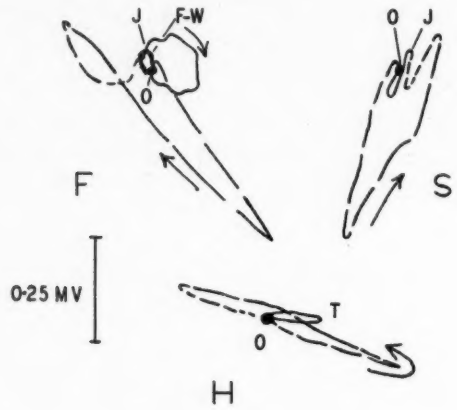

FIGURE VI

Traced drawings of VCG in a case of mitral stenosis showing the slowing of the rate of inscription of the loop in its terminal portion as it travels in to *J* from the right. Note that the direction of inscription of the horizontal loop is anticlockwise. *F-W* indicates fibrillation waves.

JT Component of the Ventricular Complex.—As *J* normally coincides with *O*, the *JT* component of the ventricular complex takes the form of a closed loop, the *T* loop. This loop is usually a narrow oval in shape. In 35 cases in the series the *T* loop was normal in this respect. Where there is a *J*-shift, the *JT* component becomes an open *U*-shaped figure, which is generally best seen in the frontal plane. It usually follows the direction of rotation of the *QRS* loop, and as this is usually clockwise, the *JT* segment also is inscribed in a clockwise direction, passing from above to the left and in to the origin. In contrast, in left ventricular hypertrophy the *JT* segment is almost always inscribed in an anticlockwise direction as viewed in the frontal plane.

TABLE III

Direction of Displacement of J *Relative to* O

Direction of Displacement of *J*	Number of Cases			Total
	Congenital Heart Disease	Mitral Stenosis	Miscellaneous	
Right	3	9	1	13
Central	2	7	4	13
Left	2	0	0	2
Forwards ..	0	1	1	2
Central	2	6	4	12
Back	5	9	0	14
Up	5	11	4	20
Central	1	5	0	6
Down	1	0	1	2

QRS-T Spatial Angle.—Normally the spatial angle between the long axes of the *QRS* and *T* segments of the ventricular complex does not exceed 40°, although it may increase somewhat with age. The angle was above this figure, usually considerably so, in 34 cases of this series—14 in the congenital group, 12 in the mitral stenosis group and eight in the miscellaneous group. Except for one patient with mitral stenosis, all these patients had an abnormal *QRS* contour. As this exception also had a *J* shift, and was taking full doses of digitalis, the effect was thought to be due to this drug.

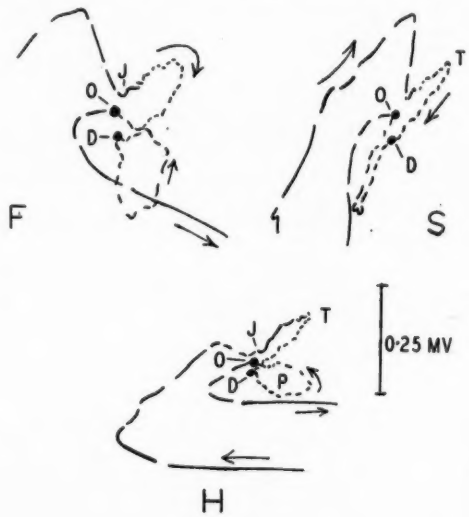

FIGURE VII

Traced drawings of VCG in a case of simple pulmonary stenosis showing shift of both *J* and *D* relative to *O*, as seen with high amplification.

D Shift.—In seven cases of the present series the light spot tracing out the vector loop paused at the end of the *JT* segment at a point which did not coincide with the origin (*O*) of the *QRS* loop. We have called this point *D*, as it represents the diastolic interval before commencement of the next auricular systole; the displacement is a *D*-shift. From *D* there is

inscribed a *P* loop which is not closed, but continues on, usually upwards, to *O*, where the *QRS* loop begins (Figure VII). The shift corresponds in the electrocardiogram to a displacement of the *TP* interval relative to the *PQ* interval. Tachycardia can cause this phenomenon, but we have observed it at normal heart rates. The heart rate of the subject whose VCG is ilustrated in Figure VII was 70 per minute. Apart from tachycardia, a prominent *U* wave or the changes of auricular strain may be responsible factors. It is not invariably associated with a large *P* loop. A *D* shift occurred in two cases of congenital heart disease, in four of mitral stenosis and in one in the miscellaneous group.

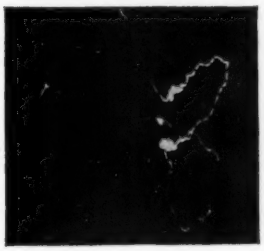

FIGURE VIIA

Photograph of the cathode ray screen from which the frontal projection of Figure VII was traced.

Digitalis Effect.—Thirty-six of the patients in this series were taking digitalis—one in the congenital heart disease group, 29 in the mitral stenosis group and six in the miscellaneous group. The effect of digitalis on the VCG is to produce a *J*-shift with a tendency for the *JT* segment to be directed away from the *QRS* loop. Thus the interpretation of the significance of a *J*-shift or increased *QRS-T* angle may be more difficult when a patient is taking digitalis. However, as has been pointed out, all but three subjects with one or both of these abnormalities had an abnormal *QRS* loop, so that their VCG's could be judged abnormal regardless of the presence or absence of digitalis effect. In only three cases, all of mitral stenosis, was it thought that digitalis alone could account for the abnormalities.

Comparison with the Standard Electrocardiogram (Table IV)

Routine scalar electrocardiograms (ECG's) were recorded in all cases. The tracings were reported as being entirely normal in three cases. A further seven subjects had abnormalities involving only the auricular complex, with abnormal *P* waves in three and auricular fibrillation in four. The remaining 58 subjects had abnormalities of the ventricular complex. These were thought to indicate right ventricular hypertrophy in 51, definite in 39, slight or doubtful in 12. Left ventricular hypertrophy was diagnosed in three cases, right bundle branch block in three (complete in two and incomplete in one), and combined ventricular hypertrophy in one.

By comparison the total VCG figures show that three were considered to be quite normal,

TABLE IV

Comparison of VCG's with ECG's

Observation	VCG	ECG
Normal	3	3
Abnormality in auricular complex only (including fibrillation)	8	7
Right ventricular hypertrophy:	52	
Definite		39
Slight or doubtful		12
Left ventricular hypertrophy	—	3
Right and left ventricular hypertrophy	—	1
Right bundle branch block only	—	3
Bizarre *QRS*	2	—
JT segment abnormality only	3	—
Total	68	68

and a further eight subjects had abnormalities only of the auricular complex, an abnormal *P* loop being present in five cases and auricular fibrillation in three. The remaining 57 subjects showed abnormalities of the ventricular complex, but in three this did not involve the *QRS* loop, the increased *QRS-T* angle or *J*-shift or both being ascribed to the effect of digitalis. Thus 54 subjects had an abnormal *QRS* loop. In 52 cases this was thought to indicate right ventricular hypertrophy; in two the significance of the abnormal pattern was uncertain. Of the 52 subjects with right ventricular hypertrophy, three had slowing of the terminal segment of the loop with prolongation of the total duration beyond 0·10 second as is described in right bundle branch block; a further 19 subjects showed a lesser degree of terminal slowing without prolonged total duration.

Thus by each method about the same number of patients were thought to have abnormalities of the ventricular complex. The interpretation placed upon these abnormalities did, however,

differ in a number of cases, and the same patients were not necessarily considered normal by both methods. Thus of the 11 patients with normal ECG's, one was considered to have VCG evidence of right ventricular hypertrophy, and one had a bizarre VCG of uncertain significance. The patient with the ECG interpretation of combined ventricular hypertrophy, and one of those with left ventricular hypertrophy, showed a VCG pattern of right ventricular hypertrophy; the other was considered to be normal. On the other hand, of the 13 patients with ECG evidence of slight right ventricular hypertrophy, three had normal VCG's and one a bizarre picture of uncertain significance. With one exception all the patients with definite right ventricular hypertrophy in the ECG also showed definite right ventricular hypertrophy in the VCG. The three patients with complete right bundle branch block were thought to have the fundamental pattern of right ventricular hypertrophy with, in addition, a conduction defect of varying degree. Apart from this last question, all except one of the disagreements occurred in cases of mitral stenosis.

DISCUSSION

In the previous paper on the VCG pattern of left ventricular hypertrophy in hypertension (Gardiner and Lowe, 1953), it was pointed out that the picture seen in the majority of cases was an abnormality of the *QRS* portion of the ventricular complex in either its position or its contour or both. The same statement can be made about the VCG pattern found in right ventricular hypertrophy. Although *J*-shift and abnormalities of the *JT* component, including increase of the *QRS-T* spatial angle may be present and provide additional evidence of abnormality, they do not show distinctive features of ventricular hypertrophy as does the *QRS* component of the ventricular complex.

In right ventricular hypertrophy the characteristic distortion of the *QRS* loop does not as a rule appear until after the first third of the loop has been inscribed. The initial crochet and part or whole of the centrifugal limb may be normal, although on the average the latter tends to be directed rather more vertically and forwards than in the normal loop. From this point the loop is directed to the right, usually forwards, and often upwards. Commonly, too, the terminal segment or "run-in" to *J* is slowed in inscription, sometimes very much so. The deviation of the loop to the right results in most cases in a contour which is distorted when compared with the smooth elongated or oval loop found in normal subjects. Even when the shape remains within normal limits, the displacement is such that it can be quickly recognized, for it produces abnormal rotation of the loop as viewed in the horizontal plane. This projection proved most useful in the recognition of abnormality in this series. Rotation of the horizontal loop was abnormal—figure-of-eight or clockwise—in 44 of the 54 cases in which the *QRS* loop was abnormal. This probably accounts for the much better correlation between VCG and ECG diagnosis in this series than in that of left ventricular hypertrophy already referred to. It was suggested in the latter that one reason for lack of correlation was that the commonest *QRS* distortion—the "fling-up" pattern— was best appreciated in the sagittal projection, which is little explored in conventional scalar electrocardiography. However, in right ventricular hypertrophy, in which it is the horizontal projection of the VCG that gives the greatest information, the ECG reveals *QRS* abnormalities with greater clarity than it does in left ventricular hypertrophy, for an approximately horizontal plane is explored in some detail by the precordial leads. Hence diagnostic information in this plane may be as readily appreciated in the ECG as in the VCG. However, the VCG gives a total picture of the *QRS* pattern, and is thus probably less liable to misinterpretation. For instance, in this series, in the three cases in which the ECG diagnosis of left or of combined ventricular hypertrophy was based on *ST-T* changes in left-sided precordial leads, the *QRS* loop pattern in the VCG gave no evidence of left-sided hypertrophy; in fact, the contour in two cases was considered diagnostic of right ventricular hypertrophy, although the rotation of the horizontal loop remained normal.

Although a high degree of correlation between VCG and ECG diagnosis of right ventricular hypertrophy has been shown to exist, exceptions do occur and are worth examination. For instance, in one case in this series the ECG was thought to indicate right ventricular hypertrophy, and yet the *QRS* loop in the VCG showed no distortion as described above. The case was one of mitral stenosis in a woman, aged thirty-eight years, with a small heart, classical signs of pure stenosis and sufficiently severe symptoms to warrant mitral valvotomy. The ECG diagnosis was based upon two of the well-known criteria of Sokolow and Lyon (1949)—namely, an *R* wave in V_1 greater than seven millimetres and an *R*/*S* ratio in this lead slightly greater than 1·0. Other criteria were not fulfilled. Thus there was no delay in the

onset of the intrinsicoid deflection in V_1, and the R wave in aV_R was only one millimetre tall. There was no deep S wave in V_6, and the ratio $\frac{R/S\ V_6}{R/S\ V_1}$ was not less than 0·4; it was, in fact, 4·7. This draws attention to certain implications of Sokolow and Lyon's criteria. An ECG pattern of R/S greater than 1·0 in V_1 can in fact correspond to two quite different patterns in the horizontal projection of the VCG, as follows:

In the first pattern there may be a forward direction of the loop axis of about 20° or more, which may be combined with bowing of the centrifugal limb forward or to the right. The changes occur in the first half of the loop, the remainder of which is normally inscribed. This would not be accompanied by a delay in the intrinsicoid deflection in V_1, nor by a deep S in V_6 or tall R in aV_R. The majority of Sokolow and Lyon's criteria are not fulfilled, as these involve later events in the inscription of the QRS complex.

In the second pattern there is a reversal of the direction of rotation of the horizontal loop, with strong deviation to the right of the centripetal limb. The R/S ratio in V_1 will be greater than 1·0, and R may be very tall, either a single wave, or more often one notched on the upstroke, or actually split into primary and secondary R waves, the latter being tall. Further than this, the intrinsicoid deflection in V_1 will be delayed, there will be a deep S wave in V_6, and if the loop is deviated upward as well as to the right, R in aV_R may be tall. Abnormality here involves particularly the latter half of the QRS loop, and thus corresponds to the abnormal patterns described above; it is undoubtedly part of the electrical phenomena associated with right ventricular hypertrophy.

The interpretation of the first pattern is more difficult. It represents a change of electrical position rather than a distortion of the loop. However, because in the case quoted it is probable that right ventricular hypertrophy did in fact exist, it may be that in an adult forward rotation alone of the QRS loop to 20° or more in the horizontal plane may be indicative of right ventricular hypertrophy, especially if accompanied by other suggestive abnormalities, such as a large P loop as occurred in this case. A horizontal angle greater than 20° occurred only once in the normal series of 68 cases, although this included a number of children.

Thus, although alterations in loop contour provide the most certain evidence of ventricular hypertrophy, it is probable that extreme positional changes of the loop may by themselves be highly significant.

SUMMARY

Vectorelectrocardiograms recorded by electronic synthesis in 68 cases of right ventricular hypertrophy are described. The cases comprised 22 of congenital heart disease, 36 of mitral stenosis and ten miscellaneous cases, including seven of pulmonary heart disease.

In general the changes seen were as follows: (i) Abnormalities of the P wave, chiefly of amplitude and contour. (ii) Abnormalities of the QRS loop: (*a*) of contour, especially a distortion to the right, forwards and perhaps upwards; (*b*) of rate of inscription, which was frequently slowed in its terminal portion when approaching J from the right; (*c*) of position in space. (iii) A shift of J. (iv) Abnormalities of the JT segment and the spatial angle between this and the QRS loop axis.

Some or all of these abnormalities occurred in combination; most characteristic was distortion to the right of the QRS loop, seen most clearly in the horizontal projection.

ACKNOWLEDGEMENTS

We wish to express our appreciation and thanks to the many colleagues and assistants who have made this investigation possible.

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HYPOPITUITARISM AND SOME DISTURBANCES OF CONSCIOUSNESS ASSOCIATED WITH IT.[1]

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IN the original description of Simmonds's disease (1914), the author described a woman, aged forty-six years, who was admitted to hospital in a state of coma. During the two days before her admission to hospital she gradually passed into an unconscious state from which she failed to recover, and she perished two days later. It was recorded that in life she often felt dizzy and had attacks of unconsciousness. Since that original account, it came to be accepted that these patients often die in coma and during life are susceptible to bouts of coma which were usually believed to be due to hypoglycæmia. More recently attention has been focused on another state of coma—so-called " hypopituitary coma ", which is encountered in Simmonds's disease (Allott and Simmons, 1951, and Summers and Sheehan, 1951), and in patients with pituitary tumours, before and after operation (Ingraham *et alii*, 1952, and Caughey *et alii*, 1951). On further study, it now becomes apparent, that there are still other types of disturbances of consciousness which develop in patients with hypopituitarism. The purpose of this report is to place on record a series of histories of patients with hypopituitarism and to draw attention to such comas and other abnormal states of consciousness as may occur. The overall management of hypopituitarism will be discussed.

CASE REPORTS

SIX CASES OF HYPOPITUITARISM DUE TO POST-PARTUM NECROSIS OF THE PITUITARY GLAND[2]

CASE I.—*A housewife, aged fifty years, had advanced hypopituitarism following septicæmia at the birth of a still-born child. With infection of the respiratory or alimentary tract she became confused and slept for two days and did not awaken to take food. She was admitted to hospital in a state of hypopituitary coma which lasted a week. With ten units of ACTH she regained consciousness in twenty-four hours. Later, when given one-quarter of a grain of morphine sulphate preoperatively, she went into a state of hypopituitary coma for two days.*

Mrs. G., a housewife, aged fifty years, was examined in consultation with Dr. M. B. Gunn at Palmerston North on July 17, 1952. When aged twenty-one years she was delivered of a still-born child and developed septicæmia. Lactation was not established, and amenorrhœa and loss of libido had persisted since that time. For thirty years she had noticed progressive deterioration in her mental and physical functions. She had been sensitive to cold, listless and drowsy after meals. Her skin had become very dry, her axillary, pubic and body hair had fallen, and her head hair had become coarse and scanty. Her appetite was poor and constipation was pronounced. After any infection, such as influenza or gastro-enteritis, she became drowsy and stated that she could " sleep the clock round once, and on one occasion twice ". On these occasions she had gone without food for as long as two days. Her mother stated that when she was in this state she seemed to be not fully conscious of her surroundings.

She was admitted to hospital in such an attack following " gastric 'flu " with vomiting and diarrhœa. Her last recollection was two days before her admission to hospital, and she said that she had not been mentally clear for about a week after her admission. She was in a state of coma and could not be roused. She was pale, sallow and dehydrated. The pulse rate was 80 per minute, and the blood pressure was 80 millimetres of mercury, systolic, and 55 millimetres, diastolic. Her skin was puffy, her head hair and eyebrows were scanty, and she had no axillary, pubic or other body hair. The cerebro-spinal fluid was under normal pressure and was normal on examination.

Intravenous injections of ACTH, 10 units twice daily, were given for fourteen days. Her condition improved within twenty-four hours, and three days later was quite rational. Her blood pressure rose to 120 millimetres of mercury, systolic, and 75 millimetres, diastolic, and she felt much improved. Testosterone, 400 milligrammes, and DCA, 100 milligrammes, were implanted, and *Thyroideum siccum*, half a grain three times a day, was then given. On this therapy she made good progress. She was more alert and less intolerant to the cold, and her head and body hair commenced to grow. On one occasion, prior to an implant, she was given an injection of one-quarter of a grain of morphine sulphate, after which she passed into a state of coma for two days.

CASE II.—*A middle-aged woman had severe hypopituitarism which followed puerperal sepsis. She was subject to faints and became comatose during a gastro-intestinal infection.*

Mrs. J. T. was a housewife, aged fifty-seven years. At the age of thirty-three years her only child was born. After parturition she developed septicæmia and lactation was not established. Since that time her menstrual periods had failed, and libido was absent. She became lethargic, and in spite of prolonged sleeps at night she was still drowsy in the daytime. She became subject to fainting attacks. About a year after her child was born her body and head hair began to fall out and she became very intolerant of the cold. Her actions and mental processes slowed, and for four or five years she had noticed increasing pallor,

[1] Received on August 17, 1953.

[2] The laboratory data for each patient are shown in Table I.

TABLE I

Laboratory Data in Six Cases of Hypopituitarism due to Post-Partum Necrosis of the Pituitary Gland

Case Number	Red Cells (per Cubic Millimetre)	Packed Cell Volume	Hæmoglobin Value. (Grammes per 100 Millilitres)	Basal Metabolic Rate	Serum Cholesterol Content. (Milligrammes per 100 Millilitres)	Urinary 17-Ketosteroids. (Milligrammes per 100 Millilitres)	Blood Non-Protein Nitrogen Content. (Milligrammes per 100 Millilitres)	Blood Sugar Content. (Milligrammes per 100 Millilitres)[1]	Insulin Tolerance Test Result[2]	Follicle Stimulating Hormone. (Mouse Units per 24 Hours)
I			11·0		420		42	(*a*) 105		
II	2·64		6·0	−10%		0·5		(*a*) 94 (*b*) 123 (*c*) 150 (*d*) 133	(Hypoglycæmic unresponsiveness and increased sensitivity	
III	4·83				220	1·1	28	(*a*) 70		
IV		36%	12·5	−3%, −5%		6·0		(*a*) 80 (*b*) 110 (*c*) 90	(*c*) 125 (*b*) 50 (*c*) 75 (*d*) 75 (*e*) 85	96 (raised)
V	3·0	30%	11·2		410	0 (two tests)	32			
VI		32%	9·9	−21%, 24%	185			(*a*) 85	(*a*) 90[3] (*b*) 50 (*c*) 60 (*d*) 70 (*e*) 80	

[1] Glucose tolerance test (50 grammes): (*a*) fasting, (*b*) after half an hour, (*c*) after one hour, (*d*) after two hours.

[2] Insulin tolerance test (0·05 or 0·1 unit per kilogram given): (*a*) resting, (*b*) after half an hour, (*c*) after three-quarters of an hour, (*d*) after one hour, (*e*) after one and a half hours.

[3] 0·1 unit per kilogram given.

breathlessness and asthenia. Three weeks prior to her admission to the Auckland Hospital she developed a gastro-intestinal infection and had persistent diarrhœa for three weeks. She became increasingly drowsy and was admitted to hospital.

The patient was well nourished, the skin was sallow and subcutaneous thickening was pronounced. She was confused, disorientated and emotional at times. She was almost completely bald. Her eyebrows were very scanty and there was no facial, axillary or body hair. The pubic hair was reduced to a few hairs on the labia. The breasts were atrophic. The vaginal mucosa was atrophic and lacked secretion, and the iodine test revealed deficient glycogen. Her blood pressure was 135 millimetres of mercury, systolic, and 80 millimetres, diastolic. The mean corpuscular volume was 83 cubic μ, and the mean corpuscular hæmoglobin was 30 milligrammes. The state of confusion cleared in two days, and with thyroid, DCA and œstrogens she made good progress. The therapy was maintained and five years later she was doing her own housework. Her head hair had grown sufficiently to enable her to discard her wig.

CASE III.—*A housewife, aged thirty-six years, had a post-partum hæmorrhage and subsequently developed hypopituitarism. She slept by day and twelve hours at night. During a respiratory infection she passed into hypopituitary coma. She was treated with testosterone and thyroid and roused in three days.*

Mrs. G. G. was a housewife, aged thirty-six years, who was referred by Dr. J. Willis. During her first pregnancy (1935), when she was aged twenty-one years, bleeding *per vaginam* began at eight and a half months, and continued for six weeks, when she went into labour. She had a severe post-partum hæmorrhage necessitating a blood transfusion. Lactation was never established and menstruation did not commence again. She had one withdrawal hæmorrhage following œstrogen therapy eighteen months later. Since 1936 her health had steadily deteriorated. Her pubic, axillary and body hair had fallen out five or six years before her admission to hospital, and for two years her head hair and eyebrows had been falling out. Her libido had failed completely after her baby was born. She had been lethargic for many years and always slept in the daytime, and in addition had twelve hours in bed every night when she slept heavily.

On December 12, 1950, she was admitted to the Palmerston North Hospital. She had become increasingly drowsy for eight to ten weeks, and a week before her admission had developed a respiratory infection and passed into a state of stupor two days later.

The patient was a well-covered woman with a pale, soft skin, which was puffy and wrinkled round the mouth. She could just be roused by shouting. Her voice was slow and "thick". Her head hair was scanty, fine and dull. Her eyebrows were scanty, and she had no axillary or body hair and pubic hair was very scanty. She was dull and slow of cerebration. The blood pressure was 100 millimetres of mercury, systolic, and 80 millimetres, diastolic. In the Kepler test, factor "A" was 5.

She was treated daily with testosterone, 25 milligrammes, and *Thyroideum siccum*, 0·5 grain, and in three days emerged from the state of stupor, but remained drowsy for a further seven days. Subsequently she had implants of testosterone, 200 milligrammes, and DCA, 100 milligrammes, and commenced treatment with *Thyroideum siccum*, three grains daily, and when examined on April 23, 1952, she was

much improved. She had a profuse growth of head hair and her axillary and pubic hair had grown. She was more alert, and said that she was less drowsy and her libido had returned.

CASE IV.—*A housewife, aged fifty-six years, developed hypopituitarism following toxæmia of pregnancy. She subsequently developed rheumatoid arthritis. After the shock of an accident she developed fever, headaches, vomiting, visual hallucinations and transitory left-sided weakness, and passed into hypopituitary coma, from which she recovered in four or five days. Several attacks of this type occurred in the course of three years.*

Mrs. E. H. was a housewife, aged fifty-six years, who was married at the age of twenty-two years, and her first pregnancy occurred fourteen years later. She had severe toxæmia and the child was removed prematurely. Lactation was not established and menstruation recommenced in four months. Fifteen months later she became pregnant again, and a girl was born after surgical induction of labour. Thereafter lactation was not established, and her menstrual periods did not recommence. In spite of this she became pregnant again, and her third child was born three years later. Lactation was not established. Scanty menstrual periods began again after this and persisted at irregular intervals. Six years later she developed rheumatoid arthritis.

Three years before her admission to hospital she was involved in a tram accident, but was uninjured. Two days later she developed headaches, vomiting, confusion and organized visual hallucinations, of different types. On occasions she was hallucinated and "saw" an animal which she recognized as a cheetah. There was also an associated weakness of the left arm and leg. This attack lasted for four or five days. She had a series of attacks of this nature, except for the hemiplegic signs, for the next three years occurring every month or two. Usually she was febrile in these attacks, but was unable to say if the fever developed before the attack. Over the past five years she had noted increasing pallor, fatigue, drowsiness, palpitations and exertional dyspnœa, and her hair fell from her body and became dry and fine on the head. For several years she had had severe thirst.

Her skin was soft and sallow, with some circumoral wrinkling. Her head hair was fine, and there was no hair on the limbs or axillæ. Very scanty pubic hair was present. She had rheumatoid arthritis involving the hands, the feet and the cervical part of the spine. No definite abnormality was detected in the central nervous system.

In a controlled twenty-four hour water-balance test there was an intake of 1485 millilitres and an output of 3888 millilitres, and the diagnosis of *diabetes insipidus* was established. The glucose tolerance curve was flattened. X-ray examination of the skull and chest gave normal results. X-ray examination of the hands and feet revealed evidence of arthritis. Encephalography and arteriography revealed no abnormality.

Testosterone, 200 milligrammes, was implanted, and *Thyroideum siccum*, 1·5 grains, was given daily. During her ten weeks in hospital she had no attacks of confusion. She has not been examined for four months.

CASE V.—*A woman, after a severe post-partum hæmorrhage, developed clinical and biochemical evidence of hypopituitarism. After the performance of the Kepler test she had a series of faints. Later, after a febrile chest complaint, she went into hypopituitary coma for two days, from which she gradually recovered. Some months later while in hospital she suddenly passed into peripheral cardiac failure with coma, and died. The post-mortem examination revealed pituitary necrosis.*

Mrs. McK., a housewife, aged fifty-three years, was admitted to the Dunedin Hospital under Professor Smirk on November 8, 1951. She had been well until her first pregnancy twenty-six years previously, when she had a severe post-partum hæmorrhage. Lactation was not established. Menstruation was reestablished a few months later, but the loss was scanty and lasted two or three days, whereas previously it had lasted five or six days and there had been a heavy loss. Five years later she became pregnant again. After parturition lactation was not established, and menstruation was never established thereafter. For twelve years she had noticed increasing fatigue and pallor, drowsiness, and a general slowing up of her physical and mental activities. She felt the cold greatly, and five years previously her body hair, head hair and eyebrows had begun to fall.

Her skin was soft and sallow and wrinkled round the mouth and chin. Her head hair was soft and fine, and her eyebrows were scanty. There was no axillary or body hair, and the pubic hair was scanty. Her blood pressure was 130 millimetres of mercury, systolic, and 70 millimetres, diastolic.

In the Kepler test, the overnight specimen was 300 cubic centimetres, the largest day specimen was 30 cubic centimetres, and factor "A" was 7. After the Kepler test she had what was thought to be a vasovagal attack, and in the following twenty-four hours she had four or five similar attacks.

DCA, 100 milligrammes, was implanted subcutaneously.

Soon after her discharge from hospital she developed a febrile illness and was confused for forty-eight hours, and her family said that she had some weakness of the right arm. She recovered gradually in the course of ten days and was noted to have desquamation of both hands.

She was readmitted to hospital on February 13, 1952, for reassessment. She was reported to be improved and "well". Her blood pressure was 130 millimetres of mercury, systolic, and 70 millimetres, diastolic. Treatment with methyl testosterone, five milligrammes, was commenced daily by mouth, and also *Thyroideum siccum*, one grain, was given by mouth. Two days later she suddenly developed peripheral circulatory failure and became semicomatose. In spite of intravenous therapy with glucose and "Neosynephrin", she died two days later.

At post-mortem examination there were 10 millilitres of straw-coloured fluid in both pleural cavities and adhesions at the apex of the left lung. The ovaries were atrophic, small and fibrous. The uterus was small. The thyroid appeared normal and the parathyroids were normal. The adrenals were atrophic. The pituitary weighed 360 milligrammes. Examination of sections revealed pronounced collagen deposition in one area. Approximately one-half of the gland had been destroyed by infarction.

CASE VI.—*A woman, aged forty-six years, developed hypopituitarism after a severe post-partum hæmorrhage. For two years she had frequent fainting turns. After the intravenous injection of a minimum amount of anæsthetic agent she passed into an advanced stage of anæsthesia from which she was slow to recover. In hospital, as a result of the stress of investigations, she developed hypopituitary coma.*

Mrs. J. McL., a housewife, aged forty-six years, was admitted to the Dunedin Hospital under the care of Professor Smirk on August 3, 1952, because of

increasing breathlessness and severe exhaustion. After the birth of her first child in 1927 lactation failed, and after her second child was born in 1928 lactation was not established and she had no return of menstrual periods. She became pregnant again in 1931, the first indication being fœtal movements. After this pregnancy she had a severe post-partum hæmorrhage, and was blind for two days; lactation was not established and the amenorrhœa persisted. After this she became increasingly fatigued and drowsy. Ten years prior to her admission to hospital her axillary, body and pubic hair fell out and her head hair became dry, fine and scanty. Breathlessness became progressively worse, and for two years she had been subject to frequent fainting turns, when she would almost "fade out" without complete loss of consciousness. Her appetite was poor and she was constipated. She reported that on exposure to cold weather she was apt to become very drowsy.

Just before her admission to hospital she had an intravenous anæsthetic for a tooth extraction. The anæsthetist stated that she had "Nembutal", 1·5 grains, for premedication, and passed to the third state of anæsthesia after three or four cubic centimetres of "Pentothal Sodium". She thereafter took two days to recover fully. The dentist stated that her teeth had all become very loose, and on their extraction there was an odour as of decaying bone in spite of minimal infection. To direct question she replied that she often became drowsy and could sleep for long periods at times when she had any infection. While in hospital, before the successful establishment of substitution therapy, she passed into a state of confusion in which she was partially disorientated as to time and place and developed auditory hallucinations. Her mood was not unduly disturbed, but her insight was impaired.

On her admission to hospital she presented a classical picture of hypopituitarism. She was very pale, and her skin was sallow, atrophic and wrinkled round the mouth. Her hands were dry and slightly œdematous. There was considerable loss of head hair, and no axillary or body hair was present. The pubic hair was scanty. The glucose tolerance curve was flattened.

Substitution therapy, commencing with ACTH, 60 units daily and reduced in ten days to 10 units daily, testosterone, 10 milligrammes daily, and *Thyroideum siccum*, 0·5 grain, led to a notable improvement, which was apparent six months later.

SIX CASES OF HYPOPITUITARISM DUE TO TUMOURS IN OR AROUND THE PITUITARY FOSSA.[1]

CASE VII.—*An elderly man had a large calcified craniopharyngioma and advanced hypopituitarism. He was very sleepy and had attacks of confusion lasting an hour or two. Also he had attacks of hypopituitary coma precipitated by infection and lasting three or four days.*

H.B. was a man, aged seventy-four years, married, with no children, who was referred by Dr. V. Cable. For twelve years he had been tired, and had lacked energy and slept a great deal. He had been subject to attacks of unconsciousness for years. In the attacks he had a giddy feeling, went unconscious for an hour or two, and then recovered. His wife reported that six years earlier he had had two fainting attacks, and in the winter of 1936 he had had an attack of bronchitis and developed coma necessitating his admission to hospital. Subsequently he had several attacks of prolonged stupor and had been treated at the Wellington Hospital on this account on at least three occasions.

In 1947 he was admitted to hospital with congestive heart failure and myxœdema and was found to be stuporose. Three days later he became more comatose, and could just be roused by shouting and answered in monosyllables. He was incontinent of urine and fæces. His blood pressure was 90 millimetres of mercury, systolic, and 50 millimetres, diastolic. He remained in this state for four days and then slowly recovered.

On September 3, 1949, he was readmitted to hospital in a stuporose state. He could be roused by shaking or by shouting and answered in monosyllables. His blood pressure was 170 millimetres of mercury, systolic, and 100 millimetres, diastolic. He slowly recovered from the stupor in three to four days.

On December 20, 1951, he was admitted to the Wellington Hospital with a respiratory infection, and passed into a drowsy semicomatose state. He was confused and incontinent of urine and fæces, and again recovered in four days. X-ray examination of the skull revealed a calcified craniopharyngioma.

The patient flew to Dunedin by the normal airways service plane. On his arrival at the hospital he was in a state of confusion and was unable to give an account of his illness. For two days he was drowsy and failed to recognize his wife. He was a slightly built, fair, grey-headed, pale man, with a fine atrophic skin, no axillary or body hair, and scanty pubic hair of a feminine distribution. The blood pressure was 114 millimetres of mercury, systolic, and 76 millimetres, diastolic. The genitalia appeared normal. He was lethargic and at times confused and disorientated. His memory was defective.

The glucose tolerance curve was flattened. X-ray examination of the skull revealed an irregularly calcified tumour arising from the floor of the pituitary fossa, which was grossly enlarged and extended upward to the neighbouring brain. Tomography showed that the lesion probably originated in the pituitary fossa and was likely to be a calcified craniopharyngioma.

Testosterone, 400 milligrammes, and DCA, 100 milligrammes, were implanted subcutaneously, and following this thyroid (1·5 grains), "Ferrivenin" (100 milligrammes) and ferrous sulphate were given. After this he became more alert and less drowsy. He gained weight and developed slight œdema and congestion. An electrocardiograph showed changes suggestive of an anteroseptal infarct. By reduction of his salt intake his weight was controlled and he was kept at rest for three weeks. He returned to his home by air, with a warning to restrict his activities. The salt intake was restricted, and ferrous sulphate (six grains three times a day) and *Thyroideum siccum* (0·5 grain three times a day) were prescribed. Three weeks after his return home he developed congestive heart failure, and he died three weeks later.

CASE VIII.—*A man, aged fifty-two years, had pituitary dwarfism, diabetes insipidus and hypopituitarism due to a large pituitary tumour. He suffered from hypersomnia.*

Mr. J. D. was an unmarried bank teller, aged fifty-two years. His growth was retarded and he had never matured sexually. He had never shaved, had never grown axillary or pubic hair, and had lacked interest in the opposite sex. For thirty years he had led an active existence as a bank clerk. As long as he could recall he had suffered from intense thirst

[1] Laboratory data for each patient are shown in Table II.

TABLE II

Laboratory Data in Six Cases of Hypopituitarism due to Tumours in or Around the Pituitary Fossa

Case Number	Red Cells (per Cubic Millimetre)	Packed Red Cell Volume	Hæmoglobin Value. (Grammes per 100 Millilitres)	Basal Metabolic Rate	Serum Cholesterol Content. (Milligrammes per 100 Millilitres)	Urinary 17-Ketosteroids. (Milligrammes per 100 Millilitres)	Blood Non-Protein Nitrogen Content. (Milligrammes per 100 Millilitres)	Blood Sugar Content. (Milligrammes per 100 Millilitres)[1]	Insulin Tolerance Test Result[2]
VII 1st Admission 2nd Admission 3rd Admission	3·3	43%	13·8	−8%, −3% −22%	260	3·1	25	(*a*) 80 (*a*) 70 (*b*) 80 (*c*) 85 (*d*) 100	(*a*) 115 (*b*) 75 (*c*) 65 (*d*) 45 (*e*) 50 (*f*) 65
VIII						9·5		(*b*) 90 (*c*) 130 (*d*) 80	(Hypoglycæmic unresponsiveness)
IX	4·1		11·46					(*a*) 80 (*b*) 100 (*c*) 100 (*d*) 100	
X		41%	13·6		295	0·5		(*a*) 70 (*b*) 80 (*c*) 90 (*d*) 90	(*a*) 70[3] (*b*) 30 (*c*) 20 (*d*) 30 (*e*) 40 (*f*) 50
XI		36%	11·6		304	0·3		(*a*) 80 (*b*) 110 (*c*) 90 (*d*) 90	(*a*) 75[3] (*b*) 35 (*c*) 35 (*d*) 30 (*e*) 30 (*f*) 50 (*g*) 65
XII		39%	11·6			5·0		(*a*) 90 (*b*) 110 (*c*) 90 (*d*) 70	(*a*) 90[3] (*b*) 75 (*c*) 70 (*d*) 70 (*e*) 75 (*f*) 80 (*g*) 85

[1] Glucose tolerance test (50 grammes): (*a*) fasting, (*b*) after half an hour, (*c*) after one hour, (*d*) after two hours.

[2] Insulin tolerance test (0·05 or 0·1 unit per kilogram given): (*a*) resting, (*b*) after half an hour, (*c*) after three-quarters of an hour, (*d*) after one hour, (*e*) after one and a half hours, (*f*) after two hours, (*g*) after two and a half hours.

[3] 0·1 unit given.

and polydipsia. He maintained that he was "one of the world's best sleepers", and that while suffering from intercurrent infections such as gastro-enteritis or influenza he might sleep throughout one or two complete days.

His height was 1·54 metres, his span was 1·62 metres, and from pubis to floor he measured 0·87 metre. He was an obese, immature male with fat distributed around the hips and the lower part of the abdomen. His skin was soft, œdematous and sallow. His head hair was grey, with no falling, and there was no body, facial, axillary or pubic hair. His blood pressure was 108 millimetres of mercury, systolic, and 60 millimetres, diastolic.

X-ray examination of the skull revealed erosion in the region of the pituitary fossa, which was enlarged and consistent with the presence of a chromophobe adenoma more on the left than on the right. The blood picture was normal. The glucose tolerance curve was flattened. The insulin sensitivity test showed hypoglycæmic unresponsiveness. The visual fields were full. The result of the Wassermann test was negative, the serum sodium content was 350 milligrammes per 100 millilitres.

Testosterone, 400 milligrammes, and DCA, 100 milligrammes, were implanted subcutaneously, and thyroid (0·5 grain twice a day) was given. When examined four months after his first implant he was much improved, had lost much of the fat about the hips and abdomen and was growing pubic hair.

CASE IX.—*A middle-aged single male had a craniopharyngioma, bitemporal hemianopia and severe hypopituitarism. After operation he passed into a hypopituitary coma, from which he slowly recovered without substitution therapy six weeks later, and in three months he was discharged from hospital.*

J.P., an unmarried labourer, aged forty-four years, had noticed increasing lethargy and drowsiness for five years. For two months he had noticed that he was unable to see objects on his left side. For a month he had complained of occipital headaches. He had always had a sparse growth of hair on the face and had never shaved more than every other day. He had recently noticed failure of potentia and loss of libido.

On physical examination he was a well-nourished man with a soft, sallow skin with a tendency to dryness. His head hair was natural and his facial

and body hair was sparse. The axillary hair was scanty, and the pubic hair lacked curl and was of a female type of distribution. The optic disks were pale, and bitemporal hemianopia was present. Visual acuity was " J.8 " on the left side and " J.6 " on the right. The blood pressure was 116 millimetres of mercury, systolic, and 70 millimetres, diastolic. X-ray examination of the skull revealed an enlarged *sella turcica* and indenting of the third ventricle. The glucose tolerance curve was flattened. The cerebro-spinal fluid was under normal pressure, and the contents were normal.

On April 13, 1951, Mr. Anthony James performed an intracapsular removal of a chromophobe adenoma. There was no intracapsular hæmorrhage. On the day after the operation the patient was restless and confused. His temperature and pulse were normal and he had no polyuria. He remained in a drowsy, stuporose state, moving about in bed and replying indistinctly to questions. He was able to obey simple commands. His blood pressure was 100 millimetres of mercury, systolic, and 60 millimetres, diastolic. His cerebro-spinal fluid pressure was 100 millimetres, the fluid was xanthochromic, and the protein concentration was 160 milligrammes per 100 millilitres. Fluids were given intravenously and intragastrically, but he failed to regain consciousness. On April 18 an exploratory operation revealed a small firm blood clot between the bone and the dura, and there was a minimal amount of clot beneath the frontal lobe. Little improvement followed operation, and thirty-six hours later he was still in the same drowsy, stuporose state and was more difficult to rouse. He was incontinent of urine and of fæces. He made some response on painful stimulation. The cerebro-spinal fluid pressure was 100 millimetres of water. On April 21, at a second exploratory operation, the frontal lobe appeared to be shrunken, but no blood clot was evident. He failed to regain consciousness after the exploration and six days later was still semi-comatose and difficult to rouse. The total non-protein nitrogen content was 24 milligrammes per 100 millilitres of serum, the serum sodium content was 342 milligrammes per 100 millilitres, and the serum potassium content was 16 milligrammes per 100 millilitres. The electrocardiogram was within normal limits. He remained in this state for five weeks, when he began to rouse and gradually improved and regained sphincteric control ; a week later he was able to sit up in a chair. He improved steadily, and on July 11 was discharged from hospital. His visual acuity in the right eye was " J.1 " and in the left eye " J.2 ", and to confrontation a left upper quadrant defect was evident. He had complete amnesia for the period of five weeks following the initial operation.

CASE X.—*A male, aged forty-seven years, had a chromophobe adenoma, visual field defects and severe hypopituitarism. After operation he passed into hypopituitary coma and actively refused food and fluids. Substitution therapy with testosterone, DCA, thyroid and salt was commenced. A week later he was much improved. In the course of an insulin sensitivity test in the post-operative period, he passed into hypoglycæmic coma, from which he recovered a few minutes after the intravenous administration of glucose. He also had two vasovagal attacks, probably due to postural hypotension.*

S.M., a bus contractor, aged forty-seven years, was admitted to the Dunedin Hospital for failing vision. Fifteen years previously he had suffered a severe bout of headache lasting a week or two. He had remained well until eight months prior to his admission to hospital, when he noticed that his vision was defective. He had never had a normal amount of hair on his chest, and his facial hair was sparse at the sides. All Axillary hair had fallen out over the last year, and his pubic hair was very scanty. For a year there had been loss of libido and failure of potentia and he had been lethargic.

The patient was a sallow-complexioned, well-developed, well-nourished man, with a full head of fine hair, sparse hair on the sides of his face, sparse hair on his limbs and none on his chest. There was a complete lack of axillary hair, and his pubic hair lacked curl and was sparse and of a female type of distribution. The gonads were small and soft, the prostate was small. His hands and feet were large, their appearance being suggestive of fugitive acromegaly. His visual acuity in both eyes was " J.2 ". Both optic disks were white, with clearly defined edges. To small objects he had complete bitemporal hemianopia with sparing of the fixation point. The rest of the central nervous system and other systems were normal. The blood pressure was 110 millimetres of mercury, systolic, and 70 millimetres, diastolic. X-ray examination of the skull showed that the pituitary fossa was greatly enlarged. An encephalogram showed that the third ventricle and basal cistern were filled and the tumour was outlined. It appeared to be larger on the left side. The cerebro-spinal fluid was under normal pressure. There was a moderate increase in the globulin content, and the total protein content was 70 milligrammes per 100 millilitres. The glucose tolerance curve was flattened. The insulin sensitivity curve showed pronounced hypoglycæmic unresponsiveness. The serum cholesterol content was 295 milligrammes per 100 millilitres.

Mr. James removed a chromophobe adenoma. The patient remained drowsy and stuporose, but could be roused to answer questions. On the third post-operative day he was very restive and actively and forcibly refused any fluid or food which necessitated tube feeding. He was incontinent of urine and fæces and continued in a stuporose state with a negativistic attitude, which made nursing difficult. His blood pressure was 106 millimetres of mercury, systolic, and 64 millimetres, diastolic. The blood sugar content was 115 milligrammes per 100 millilitres, and there was no sweating, tachycardia or vomiting. The serum sodium content was 230 milligrammes per 100 millilitres, and the serum potassium content 16 milligrammes per 100 millilitres. Two weeks after operation he was in much the same state, and the incontinence of urine and fæces persisted. He was then given an implant of testosterone (200 milligrammes) and DCA (100 milligrammes). Sodium chloride (two grammes) and *Thyroideum siccum* (1·5 grains) were given daily. Six days after the implants he was much improved, and was continent, cooperative and eating food normally. His temperature was normal and he was not excessively thirsty. He was still drowsy and had a partial amnesia for two weeks in the post-operative period. His skin was dry, and desquamation was present on the face and limbs. He was discharged from hospital forty days after the operation, feeling well and more energetic than before operation. Visual acuity was " J.2 " in the right eye and " J.1 " in the left eye. There was still an upper quadrant defect in both temporal fields.

Just before his discharge from hospital an insulin sensitivity test was carried out. Half the usual dose of insulin was administered intravenously, and within a few minutes the patient collapsed, with a rapid pulse, profuse sweating and coma with some twitching of the limbs. His blood sugar content was not estimated.

He was given intravenously 10% glucose solution and revived within a few minutes, but for twenty-four hours thereafter was drowsy, and during the day he fainted twice when he got onto his feet. From the account of these two attacks it was considered they were probably vasovagal attacks due to postural change and hypotension. He has since been maintained on implants of testosterone (200 milligrammes) at six-monthly intervals, and on *Thyroideum siccum* (0·5 grain three times a day). His present state is very satisfactory except for the hemianopia.

CASE XI.—*The patient had a chromophobe adenoma of the pituitary gland with bitemporal hemianopia and hypopituitarism. After operation he passed into a hypopituitary coma. He finally responded to cortisone and "Neosynephrin" with complete recovery. After operation he had three vasovagal attacks.*

J.H., a technical builder, aged forty-six years, was admitted to hospital on September 14, 1951, complaining of failing vision. Four years previously he noticed difficulty in seeing objects on the left side, and thereafter the vision in his left temporal field gradually deteriorated. Three years previously he had developed left frontal headaches, which were worse in the morning and throbbing in character. These cleared after several weeks. His skin had always been soft and his body hair scanty. He shaved daily, but his facial hair was sparse. His potentia and libido had always been weak, and recently had failed completely.

The patient was a well-developed, well-nourished man, with a sallow skin which was puffy about the face and wrinkled round the mouth. His head hair was fine and his facial hair was sparse. Axillary hair was completely lost, and his pubic hair was scanty and of female distribution. There was very scanty hair on the limbs and the chest. The eyebrows were normal. The gonads were small and soft on palpation. The visual acuity was 6/12 on the left side and 6/6 on the right side. To confrontation tests there was complete left temporal hemianopia and partial right hemianopia. The disks were pale on the temporal halves. The rest of the central nervous system was normal. The heart was enlarged. The blood pressure was 190 millimetres of mercury, systolic, and 120 millimetres diastolic. The cerebro-spinal fluid pressure was 140 millimetres of cerebro-spinal fluid, there was no increase in the number of cells, and the protein concentration was 60 milligrammes per 100 millilitre. The Wassermann test failed to produce a reaction in the blood and spinal fluid. X-ray examination of the skull revealed a considerable enlargement of the *sella turcica* and a few small flakes of calcium above and in front of it. The glucose tolerance curve was flattened, and the insulin sensitivity curve showed hypoglycæmic unresponsiveness.

On September 24, 1951, Mr. James partially removed a chromophobe adenoma. The patient recovered incompletely from the operation, but thirty-six hours later was confused and disorientated and incontinent of urine and fæces. He became increasingly drowsy, but could be roused by shouting and answered questions. His pulse and respiration were normal; his temperature was 103° F. Although it seemed likely that his state was due to a crisis of hypopituitarism, post-operative hæmorrhage could not be excluded, and the right frontal flap was turned down again. A small amount of clot was removed from the vicinity of the pituitary fossa. In the second post-operative period he failed to rouse, and again the frontal flap was turned down and a small blood clot was removed. On September 27 the serum sodium content was 294 milligrammes per 100 millilitres, the serum potassium content was 21 milligrammes per 100 millilitres, and the blood sugar content was 120 milligrammes per 100 millilitres. The pulse rate was 158 per minute and the blood pressure was 100 millimetres of mercury, systolic, and 70 millimetres, diastolic. The respirations numbered 40 per minute. Cortisone therapy was commenced on September 27, 100 milligrammes being given intramuscularly, and 0·5 cubic centimetre of "Neosynephrin" was given every six hours. Forty-eight hours after cortisone and "Neosynephrin" therapy was commenced there was a notable improvement in his condition. The temperature settled, and he became more alert and noticed things around him. The blood pressure rose to 160 millimetres of mercury, systolic, and 90 millimetres, diastolic. On September 30 the cortisone dosage was reduced to 10 milligrammes every six hours, and ACTH (10 units) was given twice daily. On October 2 the cortisone and ACTH therapy was discontinued. On October 3 his wound flap was found to be infected with a coagulase-positive *Staphylococcus aureus*, but his general condition was very satisfactory. He had amnesia for the duration of the crisis. On October 13 he was given a litre of blood, an implant of 200 milligrammes of testosterone, and *Thyroideum siccum* (0·5 grain three times a day). Six months later he was well and back to full work.

In the year following the last operation he had three attacks with loss of consciousness. The first occurred three months after the operation. He had been standing about making Christmas decorations, and on going to the bathroom he collapsed on the floor. He felt faint and perspired freely, but was not completely unconscious. He recovered, and was able to go back to bed of his own accord. A few days later, about fifteen minutes after having brandy and water, he had a similar attack, when he fainted away. The third attack occurred six months after the operation, in the morning while he was standing working over a drawing board. Just after morning tea he began to feel "queer", and collapsed and was found on the floor by the typist. An eye-witness stated that "he lay prone and immobile"; his face was a blanched grey colour, more sallow than grey, and his eyes were closed. After five minutes he began to recover and stirred when spoken to. After ten minutes he attempted to speak, but did not know where he was. Another witness stated that his eyes looked glassy all the colour had gone from his cheeks and his lips were blue. It was considered that the first two attacks, were vasovagal and probably the last was a very severe vasovagal attack with convulsive accompaniments.

CASE XII.—*The patient had acromegaly and chromophobe adenoma. After operation he passed into hypopituitary coma. Reexploration was followed by no improvement. When cortisone therapy was commenced, improvement was pronounced in twenty-eight hours.*

A clerical worker, aged thirty-nine years, was admitted to the Dunedin Hospital on November 2, 1951. In 1939 he was often prostrated with severe bitemporal headaches, and in the same year he consulted a dentist on account of difficulty with his bite. Eight years earlier he had noticed difficulty of vision on his left side. This was first apparent playing cricket, when he was forced to alter his stance as he was unable to see balls coming on the leg side. Although he noticed no change in his appearance, his family stated that on his return from World War II he was hardly recognizable on account of the gross changes in his face. His mother said that at this time he was always tired and limp and ready to sleep at any

time. There had been relative loss of potentia and libido for a year or more.

On examination he had the classical features of gross acromegaly, with advanced changes in the face and the upper and lower extremities. Kyphosis was present in the upper thoracic region, and he had almost complete bitemporal hemianopia with sparing of the macula. Visual acuity was 6/6 in both eyes. Both disks were pale. The secondary sex characteristics were normal. The growth of facial and body hair was normal. The cerebro-spinal fluid pressure was 120 millimetres of water, and the protein concentration was 60 milligrammes per 100 millilitres. X-ray examination of the skull revealed a very large *sella turcica*. Other skeletal changes were characteristic of acromegaly. An encephalogram showed evidence of extension of the tumour upwards and backwards. The result of the Kepler test was normal (factor " A ", 77). The serum sodium content was 330 milligrammes per 100 millilitres, the serum potassium content was 18·3 milligrammes per 100 millilitres, and the glucose tolerance curve was flattened. The insulin sensitivity curve showed some insensitivity.

The preoperative diagnosis was acromegaly and eosinophilic adenoma of the pituitary gland, which showed some evidence of being " burnt out ", as some of the biochemical findings suggested hypopituitarism. On November 19, 1951, Mr. James carried out a right frontal craniotomy and aspirated mucoid material from a large pituitary tumour. The patient regained consciousness half an hour after the operation was complete, but the following day was drowsy and difficult to rouse and had a tendency to vomit, and the same day he became increasingly drowsy, but could be roused if spoken to sufficiently loudly and would obey commands. As the drowsiness was increasing, it was decided to reexplore the operation site. An unimportant quantity of subdural clot was removed and the tumour capsule was full of blood clot, but was not under tension. After operation he failed to regain consciousness. There was no sweating or vomiting, the pulse rate was 100 per minute, the blood sugar content was 115 milligrammes per 100 millilitres, the total non-protein nitrogen content was 34 milligrammes per 100 millilitres, the serum sodium content was 297 milligrammes per 100 millilitres, the serum potassium content was 16·5 milligrammes per 100 millilitres, and the blood pressure was 100 millimetres of mercury (systolic) and 60 millimetres (diastolic).

Cortisone therapy was commenced, 50 milligrammes being given intramuscularly every six hours. Twenty-four hours later his condition had deteriorated further, and he could not be roused. Cortisone (100 milligrammes) was then given, and two hours later he regained consciousness and asked for a drink, and thereafter he steadily improved. He had an amnesia for the period of the crisis. Cortisone (40 milligrammes) was given every six hours for four more days. On November 29, testosterone (200 milligrammes) and DCA (100 milligrammes) were implanted, and the administration of thyroid (1·5 grains daily) and sodium chloride restriction to two grammes daily were begun. He made steady progress until the day of his discharge from hospital. The visual field defect was reduced.

DISCUSSION

The disturbances of consciousness associated with hypopituitarism range from states of coma to hypersomnia and drowsiness.

HYPOPITUITARY COMA

Hypopituitary coma occurred in eleven of the patients reported, and varied in intensity from semicoma and confusion to deep coma. Usually some form of stress was observed to induce the coma, though in some cases it came on gradually, without an obvious precipitating factor. In four cases the coma followed a craniotomy, in six a febrile illness was the precipitating factor, and in one an injection of morphine was the cause. In Case VI it was noted that after " Nembutal " (1·5 grains) and " Pentothal Sodium " (three to four cubic centimetres) had been given, the patient quickly passed to the third stage of anæsthesia and took two days to recover completely. The same patient reported also that on exposure to cold weather she was apt to become very drowsy. In one case the stress of flying seemed to induce a coma. In a case recorded by Haussmann *et alii* (1951), coma followed hypoglycæmic shock, and in spite of intravenous administration of glucose, persisted for a fortnight. In a patient of Oelbaum's (1952), penicillin appeared to precipitate a confused state.

The nature of the attacks was carefully observed in our four post-operative cases. The patients lay quietly, with normal pulse rate and a low blood pressure. Most could be roused by shouting or by painful stimulation. There were pronounced confusion and disorientation. The temperature was elevated in one and normal in three, which is contrary to the findings of Summers and Sheehan (1951). The corneal reflexes and all superficial and deep reflexes were usually present. Incontinence of urine and fæces occurred in all, but no grasp reflex or other primitive reflexes were observed. After recovery there was a period of complete amnesia for the duration of the coma. In two cases, auditory hallucinations occurred during the state of coma which were comparable with Oelbaum's (1952) case, in which a course of penicillin appeared to induce striking mental changes with confusion, disorientation and paranoid ideas; these disappeared after the penicillin therapy was discontinued, and recurred three weeks later during a second course of penicillin therapy. In two cases, transitory hemiplegia developed during the attack of coma.

HYPERSOMNIA

Eleven of the patients complained of hypersomnia. Drowsiness occurred after meals, and most patients slept deeply at night and for long periods such as ten or twelve hours. In

spite of this, most were drowsy in the day time and usually had a sleep in the afternoon. Hypersomnia was more pronounced during times of infection, as during influenza or gastro-enteritis. One patient (Case I) said that she had "slept the clock round twice" at such a time, and did not waken to take food. Another (Case II) described himself as "the world's best sleeper", and said that during an attack of "influenza" he slept for two days. A third patient said that he was always tired and could sleep at any time.

HYPOGLYCÆMIA

Hypoglycæmic coma occurred once in the group, and this during an insulin sensitivity test in which half the usual intravenous dose of insulin was given (0·05 unit per kilogram of body weight). Within fifteen minutes, the patient became pale, sweated, and collapsed in coma and had some twitching of the limbs. The blood sugar content was not estimated, but he regained consciousness within a few minutes when 10% glucose solution was given intravenously.

Fraser and Smith (1941) used the insulin sensitivity test and the level of urinary 17 ketosteroids as a key to the diagnosis of hypopituitarism. The estimation of the 17 ketosteroids is not without difficulty, and in inexperienced hands not always reliable, and hence there is a tendency to place more reliance on the insulin sensitivity test. Fraser and Smith state the dangers of the test, and advocate the use of half the usual dose (0·1 unit per kilogram of body weight) in obvious cases of hypopituitarism. However, it is apparent that in hypopituitarism the test carries considerable risks. Rolland and Matthews (1952) record severe hypoglycæmic symptoms after 1·5 units of insulin given intravenously to a man with hypopituitarism. Haussmann *et alii* (1951) recorded severe hypoglycæmic shock following 1·75 units of insulin given intravenously to a woman with Simmonds's disease. The patient remained in a state of semicoma for two weeks after the shock, in spite of energetic treatment. Oliver (1952) recorded a patient with a pituitary tuberculoma who perished after the administration of insulin, which was given to promote appetite.

FAINTING AND FITS

Six of the patients were subject to fainting attacks, and clinically there seems little reason to doubt that these were vasovagal attacks. These attacks occurred in the presence of anæmia and hypotension (Case II). They sometimes followed postural changes, such as rising from the sitting position. In two cases the fainting followed stress: in one, a Kepler test, when the patient fainted, and in the course of the next twenty-four hours four further fainting attacks occurred; in the other, two faints occurred on standing a few hours after a hypoglycæmic attack. We have no record of the blood pressure in this patient on the day in question. In one case fainting followed taking alcohol and standing about for some time. In one attack, in which we have an eye-witness's account, the patient's lips were blue and slight twitching of the arms was observed, which were evidently true convulsive phenomena the result of cerebral anoxæmia.

CLINICAL CONSIDERATIONS

It is apparent that all four types of disturbance of consciousness may occur if these patients are exposed to stresses such as operations, infection, hypnotics, anæsthetics, hypoglycæmia and possibly cold or a low oyxgen tension.

DIAGNOSIS

In any patient with an obscure coma, the possibility of hypopituitarism should always be considered. Usually the history and the dystrophic features, such as loss of axillary and pubic hair and skin changes, will give an indication of the underlying disorder sufficient to justify the exhibition of cortisone or ACTH.

MANAGEMENT

Infection

We have seen that infections such as influenza and gastro-enteritis are dangerous, and no doubt the same applies to other infections. No patient can hope to avoid all infections, but something can be done to reduce their frequency. Crowded gatherings should be avoided, especially at times when epidemics are known to be prevalent. Contact with acute or chronic infections should be avoided, and doctors, nurses and others associated with these patients should avoid contact if they are suffering from infection. Acute infections should be treated with appropriate antibiotics under ideal conditions of bed rest, and in the case of severe infection under a coverage of cortisone.

Anæsthesia and Surgery

General anæsthesia should be avoided if possible because of the increased susceptibility to anæsthetics, and likewise surgery should be restricted to the bare essentials. When the latter is inevitable, as in emergency abdominal or traumatic surgery, operations should be

carried out under a protective coverage of cortisone administered before and after the operation. If surgery is to be carried out in the vicinity of the pituitary gland in patients with or without evidence of hypopituitarism, consideration should be given to the advisability of giving cortisone. The effectiveness of this measure has already been demonstrated by Ingraham *et alii* (1952) in the surgery of suprasellar tumours.

Hypnotics and Analgesics

It is apparent that hypnotics and analgesics must be administered with discretion and sparingly. Morphine and like products should not be given except in extreme emergency.

Insulin

It is established that these patients are unduly susceptible to insulin. On this account insulin should not be given as a therapeutic measure or for the performance of the insulin sensitivity test except under the most carefully controlled conditions.

Other Forms of Stress

Exposure to cold and flying acted adversely on two of our patients, and these should be avoided. Thyroid given alone in big doses may raise the basal metabolic rate and thus increase the demand for the adrenal hormones, with resulting stress. It should be given under careful supervision.

Substitution Therapy

We have considered the supervision, and the treatment in the event of emergency, of patients with hypopituitarism yet untreated. It is not intended to discuss in detail the routine substitution therapy of these patients, but brief consideration will be given to the matter.

In women, occasionally a further pregnancy will relieve symptoms by increasing the output of the remaining available pituitary tissue. Pituitary implants and other pituitary hormones have been disappointing. Thyroid alone met with little success, and on occasion disastrous results followed its administration (Means *et alii*, 1940, and Lerman and Stebbens, 1942). The ill effects of thyroid therapy alone may be counteracted in part by the addition of DCA, and reduced salt intake; but Simpson (1948) gives warning of dangers inherent in this therapy.

Recently Oelbaum (1952) has reviewed the literature and discussed the place of the androgens in the treatment of hypopituitarism, and stressed the correction of gonadal deficiencies, the improvement in the sense of well-being and the anabolic effects. Williams and Whittenberger (1942) stressed the value of combined substitution therapy with thyroid extract, DCA, sodium chloride and testosterone.

We have found that in either male or female patients substitution therapy with thyroid substance, testosterone implants (100 to 400 milligrammes) and increased sodium chloride intake as required has proved the most satisfactory method of treatment. On occasions DCA implants have been used, but in general have not been necessary. The thyroid administration was commenced with small doses, which were thereafter increased if no untoward symptoms developed. Testosterone implants have been repeated at intervals of six to nine months. The DCA and salt therapy is conveniently controlled by the weight record, evidence of œdema and fluoroscopic observation of the heart.

Treatment of Coma States

Hypoglycæmic Coma.—It is important to reduce the period of shock to a minimum and hypoglycæmic coma must be treated promptly with the intravenous administration of glucose. If coma has been prolonged, the addition of cortisone therapy may prevent the development of hypopituitary coma.

Hypopituitary Coma.—Opinions vary as to the optimum therapy for hypopituitary coma. Allott and Simmons (1951) described a patient suffering from severe coma who showed little response to DCA and glucose saline solution. Cortisone therapy was then commenced, and twenty-four hours later pronounced improvement had occurred. On the other hand, Summers and Sheehan (1951) have been unimpressed with the value of cortisone or ACTH, and they found no improvement with testosterone, DCA or large quantities of glucose. However, they were impressed by the hypothermia in these patients in coma, and by the value of raising the temperature by immersion in a hot bath.

Caughey *et alii* (1951) have recorded experiences with three of the patients with hypopituitary coma quoted above. In one a good response followed six days after implants of testosterone, DCA and *Thyroideum siccum*, 0·5 grain three times a day. A second responded promptly to cortisone alone and the third to cortisone and ACTH.

Various other combinations of hormones have been used in the present cases. In two, ACTH was used with good results, but in general cortisone would seem to be the hormone of

choice. Implantation of testosterone and the administration of thyroid extract by mouth should be used as maintenance therapy.

No opportunity has yet arisen to treat a patient in hypopituitary coma by immersion in a hot bath as recommended by Summers and Sheehan (1951).

SUMMARY

Twelve patients with hypopituitarism had manifestations of disturbed consciousness including drowsiness, hypersomnia, fainting, and hypoglycæmic and hypopituitary coma.

Patients with hypopituitarism are unduly susceptible to attacks of hypoglycæmia with coma and to hypopituitary coma. Very small doses of insulin may precipitate the former, and the latter may be induced by various stresses such as infection, injury, surgery, anæsthetics, hypnotics, hypoglycæmia, exposure to cold or low oxygen tension. Hypopituitarism should be considered in the differential diagnosis of obscure coma.

In the management of patients with hypopituitarism it is important to avoid stresses such as infection, surgery, anæsthesia, hypnotics and insulin shock. In the presence of unavoidable stress such as surgery or infection, these patients should be protected by cortisone.

Hypopituitarism can be successfully treated by substitution with thyroid substance, testosterone implantations and sodium chloride. DCA may be given. Hypopituitary coma may be successfully treated with cortisone or ACTH, and subsequent implantations of testosterone and administration of thyroid substance.

ACKNOWLEDGEMENTS

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THREE ANEURYSMS OF THE DUCTUS ARTERIOSUS IN THE NEW-BORN[1]

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ANEURYSMS of the *ductus arteriosus* have been rarely recorded, particularly in the British and American literature, in which only eight cases have been found (Dry, 1921; Graham, 1940, two cases; Mackler and Graham, 1943; Gross, 1945—Case V; Pinniger, 1949; Kneidel, 1949; Lennox and MacCarthy, 1951). In this paper three further examples are described and their mode of formation is discussed.

CASE REPORTS

Case I

The mother of the patient, aged twenty-one years, was a *primipara* of blood group A, Rh-positive, and her blood did not react to the Wassermann test. The pregnancy was complicated by mild preeclampsia in the thirty-fifth week, manifested by a trace of albumin in the urine with mild œdema of the feet and ankles; however, her blood pressure remained at 110 millimetres of mercury, systolic, and 70 millimetres, diastolic. In the thirty-sixth week the membranes ruptured prematurely, and she was then admitted to hospital for further management.

Under penicillin and sulphonamide "cover" she was given medical stimulation by means of an intravenous drip administration of "Pitocin", before she came into labour two and a half days after her admission to hospital, the fœtus presenting by the vertex. After a short labour she was delivered spontaneously of a male baby weighing 2·3 kilograms, the placenta and membranes being complete and the blood loss negligible. At birth the child was described as vigorous, respirations being immediately established; but as extensive exomphalos was present the child was immediately taken to the operating theatre, where, at operation, atresia of the duodenum at the duodeno-jejunal flexure was found. A duodeno-jejunostomy was performed and the exomphalos was reduced, a 3·7 centimetre defect in the abdominal wall being repaired as far as was possible.

After the operation the child's condition remained fair until several days later, when he began to vomit. On the eighth day after his birth, and after some intermittent vomiting, he suddenly collapsed after one attack, becoming cyanosed and dyspnœic, and on clinical examination his abdomen was found to be rigid.

At a second laparotomy plastic peritonitis was found and some adhesions were divided. The child's condition then improved slightly, but early on the tenth day after his birth jaundice was noted; shortly after this he vomited and inhaled the vomitus, becoming cyanosed and shocked, with shallow rapid breathing. In spite of restorative and antibiotic therapy he did not improve, and died on the thirteenth day after birth.

[1] Received on May 12, 1953.

Necropsy.—The subject, a male child, was noted to be premature and jaundiced. There was a sutured mid-line wound and the umbilicus had been excised. Bilateral pleural effusion was present; the lower lobes of both lungs were consolidated, their colour being mottled. On examination of sections, hæmorrhagic areas were seen scattered through the lungs.

The heart was normal in size, the valves, cavities and great vessels showing their normal relations. In the anterior mediastinum, anterior to the hilum of the left lung and crossed by the recurrent laryngeal nerve, was a firm, ovoid mass measuring 2·0 by 1·5 by 1·5 centimetres in size (Figure I). This mass was found to be connected with the aorta by a four millimetre orifice (Figure II). It was also connected by a small pin-point orifice with the left pulmonary artery at its origin. A thrombus was apparent within the mass, but a fine probe could be passed from the pulmonary artery to the aorta. On examination of sections, the mass (the dilated *ductus arteriosus*) was found to be filled with dark red ante-mortem clot.

FIGURE I

Photograph showing an aneurysm of the *ductus arteriosus* (Case I); the aneurysm has been twisted slightly forwards. The lower probe is inserted into the pulmonary artery, the upper into the aorta.

The bowel was œdematous throughout, whilst widespread plastic peritonitis was present. The

stomach was dilated and thick-walled, the mucosa being œdematous and blood-stained. The duodenum was dilated, measuring two centimetres in diameter and ending blindly at the start of the fourth part, whilst in the third part of the duodenum there was a side-to-side anastomosis with the jejunum distal to the atresic few centimetres of bowel. No other obstructions were found in the rest of the bowel. The liver was green in colour, but its ducts were patent.

FIGURE II

Photograph showing an aneurysm cut in section with the thrombus removed (Case I). The upper probe is in the dilated aortic orifice of the ductus.

In the brain early abscess formation was present in both cerebral hemispheres lateral to the lateral ventricles. Examination of the remainder of the organs revealed no abnormality.

The diagnosis was considered to be bilateral pneumonia with pleural effusions, atresia of the third part of the duodenum, exomphalos, peritonitis, cerebral abscesses and aneurysm of the *ductus arteriosus*.

The heart and lungs were fixed in 10% formalin solution, after which a longitudinal block of the aneurysm was cut, extending from the almost obliterated pulmonary orifice to the widely patent aortic orifice. The block cut consisted of approximately half the aneurysm together with the thrombus which filled it. Sections were then cut and stained with hæmatoxylin and eosin, Masson's trichrome stain and Verhoeff's elastic tissue stain.

Histological examination of the ductus revealed a variety of changes. The intima and internal elastic lamina were not readily seen throughout the sections, being apparently merged with the thrombus in its outer portion. This applied particularly at the pulmonary end of the aneurysm, where intimal hæmorrhages had disrupted the intima completely. One "mound" was present towards the pulmonary orifice (Figure III), and here the intima could be identified as well as the line of the internal elastic lamina, although this did not show its usual fenestrated structure.

The media consisted mainly of muscle tissue with a proportion of elastic tissue in its outer half. Some collagen was also present here. In the muscle of the inner portion of the media there were a number of changes (Figure IV); many fibres were fragmented with extruded nuclei, whilst a number of small cystic spaces were seen; occasional areas of hyaline change were apparent, while small hæmorrhages were scattered through the media.

The adventitia consisted predominantly of collagen fibres showing some separation possibly owing to artefact formation. The *vasa vasorum* were patent and appeared normal although confined, as in the normal ductus, to the outer third of the media and the adventitia. There was no evidence of inflammatory change or even of cellular reaction to the medial changes. Histological examination of portions of the aorta from this patient revealed normal aortic structure.

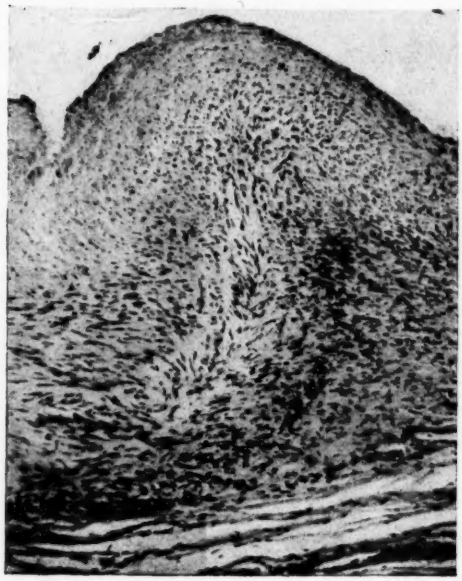

FIGURE III

Photomicrograph showing a "mound" from the pulmonary end of an aneurysm (Case I). Necrosis of the intima may be seen (some of the intima has been removed with the thrombus during preparation of the section), while early hyaline change is seen in the superficial part of the media. (×150.)

Case II

The mother of the patient, aged thirty-seven years, was having her fourth baby. Her three previous children had had normal births and were alive and well. Her blood serum did not react to the Wassermann test. She was delivered spontaneously at full term after a short labour, of a male child weighing 2·3 kilograms, the presentation being by the vertex and the delivery normal.

The child was noted to be cyanosed and dyspnœic at birth and to have a left hydrocele. On clinical

examination he was thought to have congenital heart disease; he remained cyanosed and dyspnœic until death occurred four days after birth.

Necropsy.—The head and brain were normal. The heart was normal in size, the valves, cavities and great vessels showing their normal relations. The *ductus arteriosus* was patent and rather wide throughout its length; a small intimal rupture was present at about the centre of the ductus, and there was a hæmorrhage between the layers of the wall around its whole circumference (Figure V).

The lungs contained little air, and macroscopic examination revealed many dark areas among lighter ones. Histologic examination showed that many alveoli were filled with blood. There were no other pathological findings except for a left hydrocele.

The diagnosis was dissecting aneurysm of the *ductus arteriosus* which had ruptured into the left bronchus.

No sections from this case are available for histological examination.

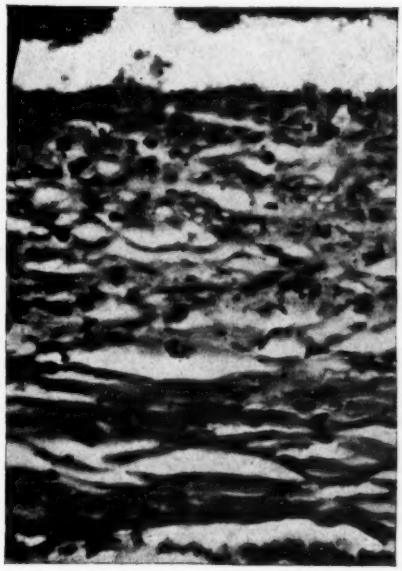

FIGURE IV

Higher power photomicrograph of the wall of an aneurysm (Case I), showing gross changes in the intima and superficial portion of the media, including the formation of cystic spaces and disruption of muscle fibres, the outermost muscle fibres being relatively normal. Portion of the intimal thrombus may be seen. (×350.)

Case III

The mother of the patient, aged twenty-nine years, was having her second child. Her blood group was A_2, Rh-positive, and her blood serum did not react to the Wassermann test. The first child had been delivered spontaneously and weighed 3·4 kilograms. This pregnancy had been complicated at the thirty-sixth week by an accidental hæmorrhage which necessitated the patient's admission to hospital, where her blood pressure was found to be 140 millimetres of mercury, systolic, and 90 millimetres, diastolic, and her urine clear. After several days' observation of the patient the membranes were artificially ruptured, and after a short labour she was delivered normally of a male child weighing 2·5 kilograms. The placenta was normal in size, but it contained one large and several small infarcts. The child breathed immediately at birth and was considered to be a normal premature baby.

FIGURE V

Photograph of the specimen from Case II, showing a dissecting aneurysm (D) of the *ductus arteriosus*. The ductus is a wide bore tube with a hæmorrhagic wall, linking the aorta (*A*) and the pulmonary artery (*P*). The wall of the ductus has been dissected apart and there is an intimal rupture.

Five days after birth the child, which previously had been sucking well, was noted to be "snuffly" and cyanosed at times, with a raised respiratory rate and mild bilateral rib retraction. He was given prophylactic treatment with streptomycin and penicillin.

Early next morning the child was distressed by oral feedings, his temperature started to rise and his respirations became rapid and shallow. Later in the morning the baby became suddenly pale and cyanosed, with irregular gasping respirations. He was noted

to be jaundiced and dehydrated, and bilateral rib retraction was more in evidence. His temperature rose to 104° F. and death occurred seven days after birth with the clinical signs and symptoms of severe bronchopneumonia.

Necropsy.—The subject was a small, premature male child weighing 2·3 kilograms, pale and slightly jaundiced.

The head, neck and brain were normal. The left lung had a mottled surface but contained air. All lobes of the right lung contained little air, while large,

FIGURE VI

Photograph of an aneurysm of the *ductus arteriosus* (Case III) showing the thrombus *in situ*. The small constricted pulmonary end may be seen at the lower margin of the aneurysm.

dark-coloured, depressed areas were obvious on the lateral surface of the lung as well as on the diaphragmatic surface of the lower lobe.

The heart was normal in size, the cavities, valves and great vessels showing their normal relations. The *ductus arteriosus* was firmly closed for four millimetres from the pulmonary end, whilst the aortic orifice of the ductus was patent, measuring three millimetres in diameter. That portion of the ductus nearest the aorta was dilated, forming an aneurysm one and a quarter centimetres by one centimetre by one centimetre (Figure VI). Examination of sections showed that the aneurysm was filled with firm ante-mortem thrombus, whilst the wall of the ductus was thicker than in Case I. No further abnormality was detected during the remainder of the necropsy.

The diagnosis was considered to be bronchopneumonia and aneurysm of the *ductus arteriosus*.

On histological examination again a wide series of changes could be seen. The endothelium of the intima and the thrombus were fused together, but the internal elastic lamina was prominent. At the pulmonary end of the aneurysm a subintimal hæmorrhage was apparent, and this had extended into the superficial portion of the media (Figure VII). One mound only was present, and this was again apparent at the pulmonary end. Below the intima was a wide bank of somewhat structureless collagen and elastic fibres, with no nuclei but a number of small cystic spaces.

Examination of the inner portion of the media revealed disruption of muscle fibres with loss of nuclei, the formation of cystic spaces and some small hæmorrhages (Figure VIII). The outer portion of the media and the adventitia appeared normal, the *vasa vasorum* being patent but not congested. There is no evidence whatsoever of acute or chronic inflammatory change, whilst the aorta was of normal structure.

Histological examination of the lung revealed severe bronchopneumonia.

DISCUSSION

There are now in the literature, including the present three cases, at least 36 records of aneurysm of the *ductus arteriosus*. All except six of these were found in infants in the age group extending from a few days to two months. Those aneurysms reported in adults form a heterogeneous group probably of various origins,

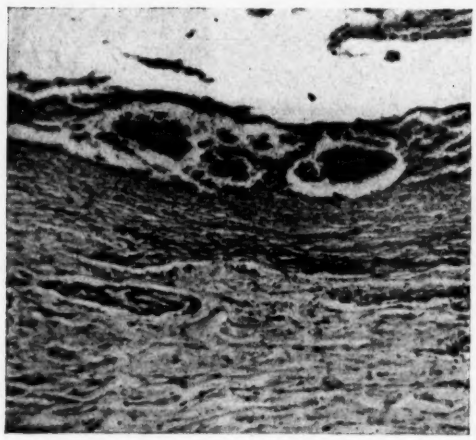

FIGURE VII

Photomicrograph of the wall of an aneurysm of the ductus (Case III), showing gross subintimal hæmorrhage extending into the superficial portion of the media. (×75.)

and do not appear to have arisen from the type of infantile aneurysm under consideration here, and hence they are excluded from the discussion. They are, nevertheless, important as a diagnostic problem and as an operative hazard for the thoracic surgeon.

Most of the infantile aneurysms of the *ductus arteriosus* have been found accidentally at post-mortem examination, the patient having died from some other disease; but in eight cases (Roeder, 1901, two cases; Guggenheim, 1930;

Esser, 1902, two cases; Fritz, 1933; Scheef, 1939; and the present Case II), death was directly due to rupture of either a saccular or a dissecting aneurysm.

Any discussion of the pathogenesis of this condition must be based on an understanding of the normal behaviour of the *ductus arteriosus* after birth.

The Normal Ductus and Its Closure

The *ductus arteriosus* is a tube some 10 to 15 millimetres in length extending from the left pulmonary artery immediately beyond its origin to the underside of the aortic arch opposite the origin of the left subclavian artery. It enters the aorta at an acute angle between 25° and 37·5° (Mancini, 1951). Its diameter is from four to eight millimetres. On histological examination it has an intima, a well-defined internal elastic lamina, a media and an adventitia. In the intima there are a number of mounds which project into the lumen, and which contain at birth fine elastic fibres and smooth muscle and later collagen. The media, while containing a small number of fine wavy elastic fibres, consists predominantly of smooth muscle, in contrast to the aorta. The outer portion of the media is the furthest point to which *vasa vasorum* penetrate. The adventitia, poorly demarcated from the media, contains abundant collagen elastic fibres and vessels with some muscle.

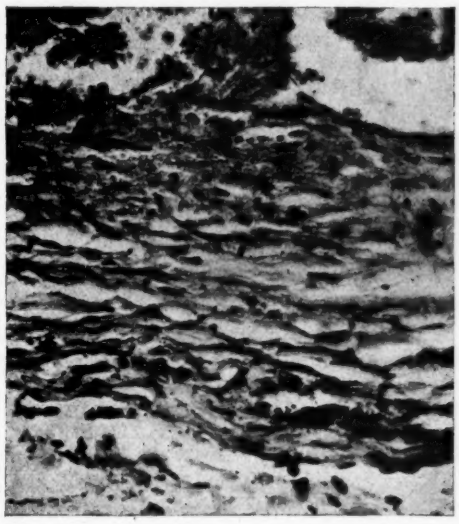

FIGURE VIII

Higher power photomicrograph of the wall of the aneurysm (Case III), showing hæmorrhage and necrosis of the muscle fibres in the superficial portion of the media. (×350.)

The mechanism of closure of the *ductus arteriosus* after birth has excited controversy for many years and must still be considered *sub judice*. At first thrombosis was considered to be the immediate cause of closure. However, this is rare, as Bettinger (1932) has shown, and is not now considered as part of the normal mechanism of closure. Strassmann (1893–1894) then postulated closure by means of a valve-like intimal fold in the ductus near the aortic opening. Roeder (1901) first noted the acute angle at which the ductus joined the aorta—a fact which would assist the valve action of the intimal fold. A further hypothesis introduced by Schanz (1888) postulated that obliteration of the ductus was attained by active sustained muscular contraction. Support for this hypothesis derives from the work of Barclay *et alii* (1938), who used angiography on lamb fœtuses delivered by Cæsarean section. They found that the ductus closed shortly after birth (in one case in five minutes) even in the absence of respiration and without interruption of the maternal circulation. They found that the pulmonary end was the first portion to close.

Histological Changes in the Ductus After Closure

Several workers, in particular Jager and Wollenman (1942), have demonstrated the changes which occur in the histological structure of the ductus with increasing age. Little change occurs in the first seven to ten days except for an enlargement of the intimal mounds. From this time on a number of appearances may be seen. Anatomical closure is effected by further increase in the size of the intimal mounds. There is fibrosis in the inner portion of the media, and this is also found in the mounds. As a result of fibrosis of such areas the media becomes more compact and slightly thicker with increased collagen and elastic tissue. In the penultimate stage of closure a small slit-like lumen may occasionally be seen in adults; the ductus is represented by a mass of dense elastic and hyaline material with a very small amount of muscle. Calcification, cartilage and even bone formation may be observed in older people. Jager and Wollenman (1942) make several interesting and important observations on the condition of the ductus in their series of 71 cases. First, a thrombus is occasionally found in the lumen of the constricted ductus which otherwise has

normal structure for its age. Secondly, in four cases they observed dissection of blood through the layers of the ductus almost to the adventitia in the mid-portion of cylindrical examples, whilst in one case there was mucinous change with cyst formation in the media. Both these authors and Blumenthal (1947) state that necrosis of the media occurs often as early as eight days after birth.

The conditions of aneurysm and dissecting aneurysm of the *ductus arteriosus* may be regarded as a type of patent ductus. Most often the ductus remains patent because of some malformation of the pulmonary artery or aorta, which necessitates blood flow through the ductus to the pulmonary or peripheral circulation. Occasionally the ductus remains patent in the absence of any other cardiac anomaly, and here the only ætiological agent so far identified is rubella in the mother during the first two months of pregnancy. In most cases of aneurysms of the ductus no other cardiac anomalies are observed, although other developmental defects may be observed; thus the subject in the first case in this paper had exomphalos, while the subject in the second case had a hydrocele.

There is in the literature no constant pathological finding to which formation of an aneurysm of the *ductus arteriosus* may be attributed. Infection has been advanced by some of the earlier workers as a possible explanation. However, Lennox and MacCarthy's (1951) case appears to be the only example of a true mycotic aneurysm. This was secondary to umbilical sepsis, though even here the aneurysm could conceivably have antedated the infection. Kaufmann's (1929) case was thought by the abovementioned authors to be similar to theirs, but in few if any others can infection be considered as having a causal relationship with an aneurysm.

Esser (1902) found hæmorrhages in the media of the wall of a ductus aneurysm. Fritz (1933) also found hæmorrhages in the wall of a ductus which had ruptured, although no aneurysm was present. This last case and Roeder's (1901) second case are the only examples comparable to Case II in this paper.

It is noteworthy that in no case so far described have any of the large vessels been reported as abnormal. Thus the aorta had a normal histological appearance in Cases I and III and on macroscopic examination was normal in Case II, so that the ætiological factor or factors may be localized to the *ductus arteriosus*. At the same time it will be remembered that localized lesions occur in conditions in which a generally acting factor is present (as in the local bone lesion of hyperparathyroidism). In the present cases there may be some more generally active stimulus (apparent in cases of extensive dissecting aneurysm of the aorta), the localization of which is determined by conditions of growth and change occurring in the wall of the ductus.

The site of most of the saccular aneurysms, as in Case I, is usually at the aortic end of the ductus, the aortic opening being widely patent. Portion of the thrombus present within the aneurysm may protrude into the aortic lumen, whence embolic phenomena are possible. The pulmonary orifice of the ductus is usually constricted to a pin-point, and this observation may be correlated with the work of Barclay *et alii* (1938), who showed that the pulmonary end constricted down first. Kneidel (1949) illustrates this point well in a post-mortem angiogram of an aneurysm of the ductus. As far as one can ascertain, no ante-natal aneurysm of the ductus has been described; this indicates again that aneurysm formation is a problem arising during closure of the ductus, and that an aneurysm probably follows an aberration in the mechanism of closure of the ductus which may be complete lack of or inefficient muscular spasm.

From a study of the " normal " closure of the ductus, there are sufficient deviations in the histological pattern (Jager and Wollenman, 1942) to explain aneurysm and dissecting aneurysm formation, given that initial muscle contraction is absent or inefficient. In the present Case II, lack of muscle spasm in primary closure followed by an exaggeration of the normal processes of closure resulting in necrosis of the media may be postulated as the sequence of events leading to the formation and rupture of the dissecting aneurysm found at necropsy.

Since rupture is a rare event, the probable fate of most of these aneurysms in the event of the patient's living would appear to have some bearing on the paucity of records of aneurysms of the *ductus arteriosus* in the literature. The answer, as Lennox and MacCarthy (1951) point out, is probably to be found in the ultimate organization and fibrosis of the thrombus with the obliteration of the ductus. If recanalization also occurred, the result would be difficult to detect from an ordinary patent *ductus arteriosus*.

SUMMARY

Three cases of aneurysms of the *ductus arteriosus* in the newborn are described—two saccular aneurysms and one dissecting aneurysm which ruptured into the left bronchus.

Histological studies were made in two cases. The intima and internal elastic lamina were merged with the thrombus, subintimal hæmorrhages and necrosis were present in the intimal mounds, and the media consisted mainly of muscle tissue in which were found fragmentation of fibres with extrusion of nuclei and scattered hæmorrhages. The *vasa vasorum* were normal and there was no inflammatory change. The aorta was normal.

These changes are similar to those which have been described in normal closure of the ductus.

It is postulated that commonly aneurysms of the *ductus arteriosus* in the newborn are produced by simple exaggeration of changes found during normal closure of the ductus, and that they may, if the patient lives, regress in the same manner as a normal ductus.

ACKNOWLEDGEMENTS

I wish to record my sincere thanks to Dr. E. Abrahams, Pathologist to the Queen Victoria Hospital, Melbourne, for the specimens and details of Cases I and III, and Dr. H. Bettinger, Pathologist to the Women's Hospital, Melbourne, for the specimen and details of Case II. I am indebted to Miss M. Johnson, Clinical Photographer to the Women's Hospital, Melbourne, for Figure V.

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ADDENDUM

Since this paper was written two other cases have been observed. The first aneurysm was in a baby, aged five days, and did not differ significantly from those in Cases I and III above. The second aneurysm was in a baby, aged nine weeks, and was found to be thrombosed, with much fibrous tissue already present. This finding supports the hypothesis proposed above, that aneurysms of the *ductus arteriosus* may be quite common, but are not observed at autopsy in older people, since the ductus aneurysms fibrose and regress in the same manner as a normal ductus. Both these patients died of intercurrent disease, the aneurysms being incidental autopsy findings. I would thank Dr. E. Abrahams, of the Queen Victoria Hospital, for these two further specimens.

A TECHNIQUE FOR ASPIRATION BIOPSY OF THE KIDNEY.[1]

R. A. JOSKE[2]

From the Clinical Research Unit of the Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital

DESPITE the known value of biopsy methods in the investigation of hepatic disease, blood dyscrasias and neoplasms, little attention has been paid to renal biopsy as a method of clinical investigation of renal disease. Some biopsy studies of the kidney have been made during the operation of sympathectomy for hypertension (Castleman and Smithwick, 1943), but the results have correlated poorly with the clinical picture of the patient, and the natural history of the disease. The kidneys have been thought to be "silent, inaccessible, and immobile". (Editorial, 1952.)

In 1951 Iversen and Brun described a technique by which satisfactory biopsy material was obtained from the kidney in 42 of 68 patients on whom renal biopsy was attempted. They subsequently described their findings in the nephrotic syndrome (Bjørneboe *et alii*, 1952*a*) and in *calcinosis renis* (Bjørneboe *et alii*, 1952*b*).

The present paper describes a technique of aspiration biopsy of the kidney, basically similar to that of Iversen and Brun, which has been developed in the Clinical Research Unit of the Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital, and illustrates the possible value of the method by two brief case reports.

TECHNIQUE

The right kidney is used as the biopsy site, to avoid possible damage to the spleen and large blood vessels adjacent to it. Biopsy is undertaken only in the absence of clinical or laboratory evidence of any bleeding tendency, if the hæmoglobin value is above 10·0 grammes *per centum*, if there is no evidence of local infection in the biopsy site, and if there is no obstruction to the flow of urine from the right kidney. The patient is admitted to hospital for performance of the biopsy.

A Franseen needle, developed originally for liver biopsy, is used. This is a hollow needle with a central stilette, 6·5 centimetres long, 2·0 millimetres in internal diameter, 2·4 millimetres in external diameter, and terminating in a serrated cutting edge.

The difficulty of renal biopsy lies in correct localization of the kidney. This is achieved by intravenous (occasionally retrograde) pyelography, with films taken in the antero-posterior and lateral positions. From these plates the position of the kidney is mapped against the lower ribs and the lumbar part of the spine, and the site of insertion of the biopsy needle is ascertained. The biopsy is made from the lateral approach. Although the kidney presents a larger surface area to a posterior approach, it is thought that the latter increases the hazard to the patient and gives a less satisfactory specimen. The skin incision is normally made just anterior to the posterior axillary line, in the tenth or eleventh intercostal space (Figure I). At this level, the kidney lies about three centimetres from the surface.

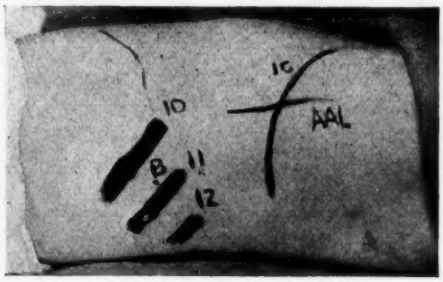

FIGURE I

Site of insertion of the needle for performance of aspiration biopsy of the kidney. AAL, anterior axillary line; B, biopsy incision; IC, iliac crest; 10, 11 and 12, ends of tenth, eleventh and twelfth ribs respectively.

At the time of biopsy the skin is sterilized and infiltrated with a local anæsthetic agent (2% "Procaine" solution). The infiltration is carried down to and includes the renal capsule with further local anæsthetic, a fresh needle and syringe being used. A small

[1] Received on October 23, 1953.

[2] Working with the aid of a grant from the National Health and Medical Research Council of Australia.

incision, about 0·5 centimetre long, is then made in the skin.

The biopsy needle with stilette in place is then inserted until it meets the renal capsule. With a little experience, the "feel" of the kidney is distinctive—the capsule is fibrous, there is a big movement with respiration, and the parenchyma is slightly "tougher" than liver tissue. The kidney normally moves up to 5·0 centimetres with respiration (Kaminsky *et alii*, 1953).

III) shows the "Lipiodol" mass to lie about 2·0 centimetres behind the kidney. A second biopsy attempt was made 2·0 centimetres further forward, and a suitable specimen of renal tissue obtained. This procedure is only occasionally needed.

When the biopsy needle is correctly placed, the patient is instructed to cease breathing, the needle pushed just through the renal capsule and the stilette withdrawn. A core of renal tissue is cut by advancing the needle with a

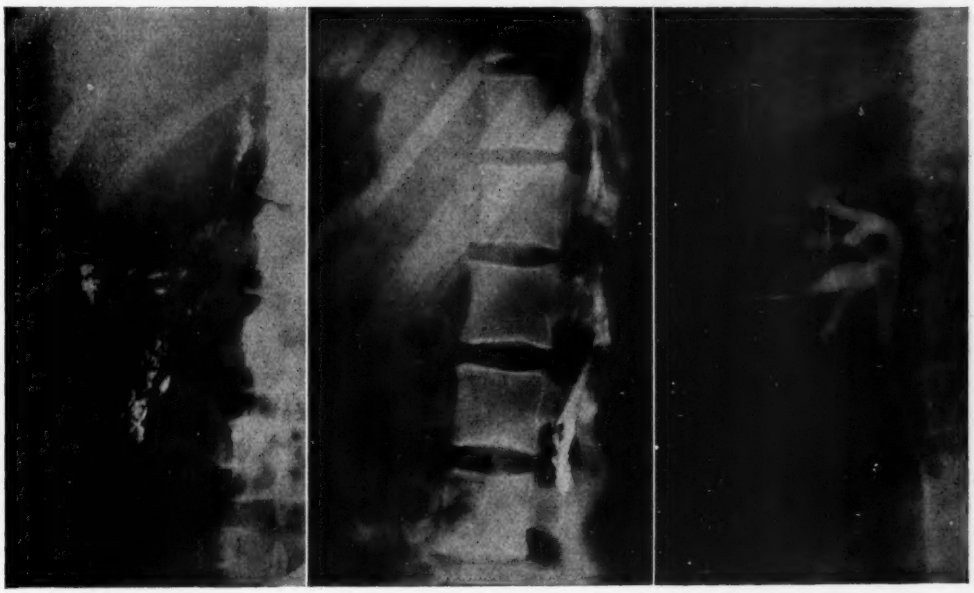

FIGURE II

An X-ray film showing distribution of "Lipiodol" injected through the needle after an unsuccessful attempt at renal biopsy. The "Lipiodol" lies horizontally along the needle track, and has spread up and down the lateral margin of the *psoas major* muscle.

FIGURE III

An X-ray picture in the lateral plane taken at the same time as Figure II. The "Lipiodol" mass lies behind the kidney, which overlies the vertebræ bodies. A second biopsy attempt with the needle 2·0 centimetres anteriorly resulted in the obtaining of a suitable specimen of renal tissue.

FIGURE IV

Simultaneous right retrograde pyelogram and aspiration biopsy of the kidney. The needle lies within the renal substance, but away from the large hilar vessels.

If there is difficulty in locating the renal capsule, 0·5 cubic centimetre of "Lipiodol" is injected through the needle, and further antero-posterior and lateral radiographs are taken. From these pictures the error of position is corrected. Such an instance is shown in Figures II and III. In the antero-posterior film (Figure II) the "Lipiodol" lies horizontally along the track of the needle, and has spread up and down along the lateral border of the *psoas major* muscle. The lateral film (Figure

rotary movement, suction is applied by an oiled 10 cubic centimetre Luer-Lok syringe containing a few millilitres of sterile normal saline, and the needle withdrawn. If the biopsy is successful, a core of renal tissue up to 2·0 centimetres long is obtained, and immediately transferred to fixative solution.

To minimize the risk of post-biopsy hæmorrhage, the patient lies still in bed for four hours, and is not allowed up until the next day.

Figure IV shows a simultaneous right retrograde pyelogram and renal biopsy. The point of the needle lies within the kidney, but is well removed from the major blood vessels. The result of this biopsy is illustrated below (Case II).

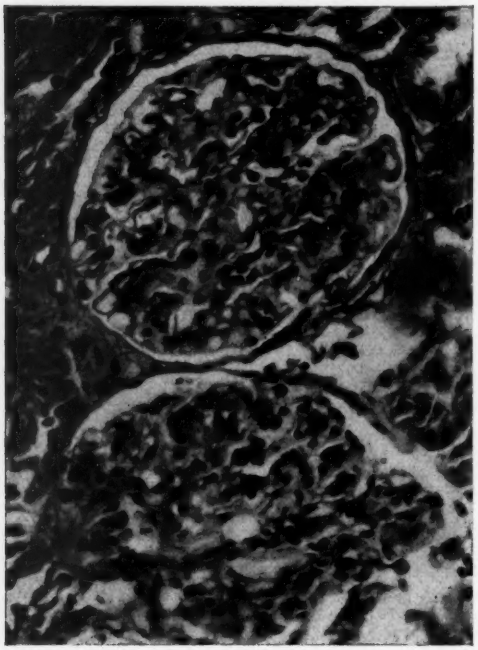

FIGURE V

Renal biopsy specimen obtained from a patient with the nephrotic syndrome (Case I). Two representative glomeruli are shown which are of normal size and appearance. There is no thickening of capillary basement membranes, the capillaries are patent and contain blood, and a juxtaglomerular arteriole to the bottom of the figure is normal. (Weigert Van Gieson stain. ×320.)

DISCUSSION

To date, biopsy attempts have been made on 30 patients and renal tissue obtained from 25. In two cases this tissue did not provide a satisfactory specimen for histological examination, in one because it was too small, in the other because only medullary tissue was included in the specimen. With increased experience, improved results are being obtained.

The patient suffers little discomfort from the procedure, except for a slight soreness at the skin site. No adverse sequelæ such as hæmaturia have been observed. Opportunity has not arisen for operative or post-mortem examination of the biopsy site in any patient so far subjected to biopsy.

The possible value of renal biopsy is not yet known. At present it is to be regarded as a method more suitable for research than for routine investigation of patients with primary renal disease or systemic disease affecting the kidney, such as *diabetes mellitus*. Renal pathology is notoriously uneven in its distribution, and it may be that the " sampling error " of renal biopsy will militate against its usefulness. In hypertension, operative renal biopsy has been of disappointingly little prognostic value, but this may not apply in so great a degree to primary renal disease. Very little work on renal biopsy has been published, and much more is required before the role of the method in clinical investigation is fixed.

FIGURE VI

Low power view of renal biopsy specimen obtained from a patient with diabetic renal disease (Case II). The figure shows how a useful amount of renal cortex may be obtained. (Weigert Van Gieson stain. ×45.)

However, increasing use of aspiration biopsy of the liver has greatly enlarged its scope of application, from primary hepatic disease to a

variety of generalized infections and intoxications, such as miliary tuberculosis, beryllosis and sarcoidosis. Similar considerations may apply to renal biopsy. In addition, biopsy methods have the great advantage that they enable the evolution of a disease process to be followed histologically in a single patient, so that a picture of the natural history of the disease can be obtained, and a precise histological diagnosis made.

To show the possible value of renal biopsy in clinical practice, two cases are reported, in both of which precise diagnosis and thus prognosis depended upon histological examination of a renal biopsy specimen.

CASE I.—C.J., a male patient, aged forty-eight years, was admitted to hospital on June 14, 1953. Three weeks previously he had noted swelling of his feet and ankles, which persisted for two weeks despite rest in bed and a diet low in salt. He had observed his urine to be "cloudy", but gave no history of nocturia or hæmaturia. He was a glassblower by occupation, and had had no drugs or injections before his admission to hospital. His exercise tolerance had been good until the onset of œdema.

He was pale, and had pitting œdema of his ankles and over the sacrum posteriorly. His blood pressure was 140 millimetres of mercury, systolic, and 100 millimetres, diastolic. The heart was not enlarged. The fundi were normal. Persistent heavy albuminuria was present.

The results of investigations were as follows. The hæmoglobin value was 15·0 grammes *per centum*, and the white cell count was 12,000 per cubic millimetre. An X-ray examination of the chest revealed no abnormality. The Wassermann test failed to produce a reaction. In the Congo red test, 95% of the dye was present seventy minutes after injection. Microscopic examination of the urine revealed occasional pus cells, but no red blood cells or organisms. The total serum protein content was 4·4 grammes *per centum*; the albumin content was 1·9 grammes *per centum*, the globulin content 2·5 grammes *per centum*, and the γ globulin content 0·8 gramme *per centum*. The serum cholesterol content was 435 milligrammes *per centum*. The fasting total serum lipide content was 1240 milligrammes *per centum*. A urea concentration test showed the blood urea content to be 39 milligrammes *per centum*; the urinary urea was 3·73%; the urea clearanc Foweather) was 104% of the average normal. A intravenous pyelogram revealed normal dye excretion by both kidneys with normal pyelograms.

The patient thus had the "nephrotic syndrome", which may result from various causes. The results of the Wassermann test and the Congo red test excluded syphilis and amyloidosis. There was no history of exposure to drugs such as mercurials. The clinical diagnosis was therefore subacute nephritis (type II of Ellis) or primary or "idiopathic" nephrosis. Renal biopsy was performed in order to assess the stage and severity of the disease.

This biopsy was reported by Dr. E. S. Finckh as follows (Figure V).

"The section includes eleven glomeruli. In these the tuft capillaries are patent and the basement membranes are not thickened. The convoluted tubules appear normal, there is no excess fibrosis and the arteries and arterioles show no change. Kidney—normal."

It was therefore considered that this patient was suffering from primary nephrosis, and that the disease was not advanced. His course to date is in keeping with this diagnosis. His œdema subsided without specific therapy, and he has returned to work. There is still a minor degree of albuminuria, but his serum albumin value has risen to 2·8 grammes *per centum*. He has no peripheral œdema.

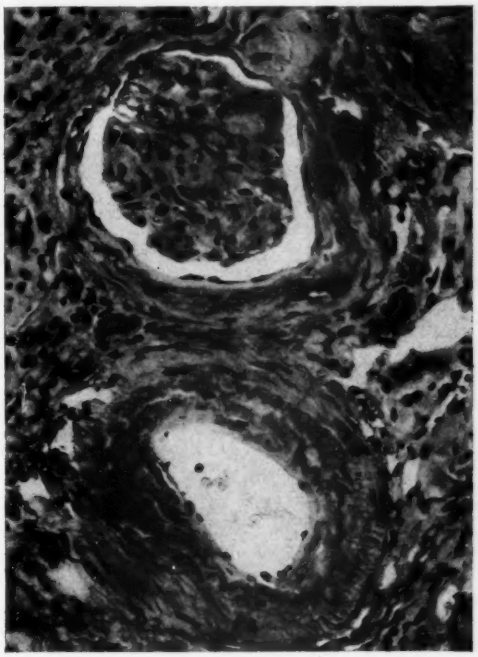

FIGURE VII

Renal biopsy specimen obtained from a patient with diabetic renal disease (Case II). The glomerulus has a thickened capsule and a hyalinized juxtaglomerular arteriole; a single hyalinized nodule is seen in one tuft, illustrating the nodular form of diabetic glomerulosclerosis. The adjacent small artery shows intimal proliferation and reduplication of the internal elastic lamina. (Weigert Van Gieson stain. ×320.)

CASE II.—C.B., a female patient, aged seventy-one years, was known to have had *diabetes mellitus* for at least ten years, but had remained in fair health except for repeated skin infections, which had responded to chemotherapy. Four years ago she was found to have albuminuria, and this was persistently present thereafter. Her insulin requirement gradually decreased from 68 to 36 units daily. She had recent dyspnœa on exertion, œdema of the ankles and blurring of vision. Her mother had died of *diabetes mellitus*.

She was obese (86·5 kilograms) and dyspnœic. Her blood pressure was 205 millimetres of mercury, systolic, and 100 millimetres, diastolic; the heart was

enlarged and a harsh systolic bruit was audible in all areas; there was slight peripheral neuritis; in the fundi advanced diabetic retinopathy was to be seen.

The results of investigations were as follows. The total serum protein content was 7·2 grammes *per centum*, the albumin content was 3·1 grammes *per centum*, the globulin content was 4·1 grammes *per centum*, and the cholesterol content was 234 milligrammes *per centum*. The total fasting serum lipide content was 490 milligrammes *per centum*. On microscopic examination of the urine, numerous pus cells were present; culture of urine produced a growth

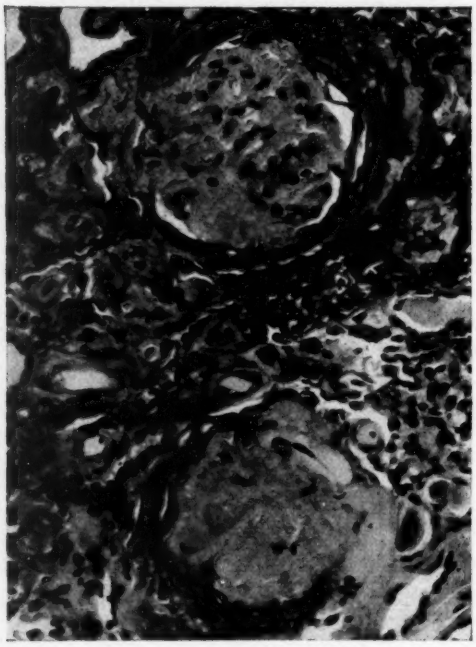

FIGURE VIII

Two further glomeruli from the renal biopsy shown in Figures VI and VII. The glomerulus above shows diffuse "intercapillary" sclerosis, which has produced almost complete obliteration of the capillary lumina. The glomerulus below shows a later stage of the same process, with almost complete glomerular hyalinization. (Weigert Van Gieson stain. ×320.)

of *Bacterium coli*. The blood urea content was 64 milligrammes *per centum*, the urinary urea was 1·8%, and the urea clearance (Van Slyke) was 38%. Intravenous pyelography revealed poor dye excretion by the left kidney and no dye excretion by the right kidney.

A clinical diagnosis was made of diabetic glomerulosclerosis (Kimmelstiel-Wilson) and generalized atherosclerosis with hypertension.

A renal biopsy was performed after retrograde pyelography (Figure IV), and Dr. E. S. Finckh reported as follows (Figures VI, VII and VIII):

"The biopsy includes twenty-four glomeruli, all of which show some degree of abnormality. A number of these are completely hyalinized; most show capsular thickening and varying degrees of hyaline thickening of capillary basement membranes. In some this affects the glomerulus uniformly producing considerable occlusion of the glomerular capillaries, but in others the change is nodular and localized to one capillary loop. The juxtaglomerular arterioles show considerable hyaline thickening, and in a number the lumen is almost occluded. Small and medium size arteries show slight atherosclerotic intimal proliferation. There is increased intertubular fibrosis, some tubular atrophy and dilatation, and many tubules contain hyaline casts.

Kidney — diabetic glomerulosclerosis, arteriolosclerosis, and slight atherosclerosis."

In this case renal biopsy confirmed the clinical diagnosis of advanced diabetic renal disease. This histological diagnosis is essential if accurate assessment of albuminuria is to be made in patients with *diabetes mellitus*.

SUMMARY

A technique is described for the performance of aspiration biopsy of the kidney by means of a Franseen needle, after localization of the kidney by intravenous (occasionally retrograde) pyelography.

Successful biopsy specimens have been obtained from 25 of 30 patients on whom biopsy was attempted.

The value of the method is illustrated by two case reports.

ACKNOWLEDGEMENTS

My sincere thanks are due to Dr. Barbara Wood, Radiologist to the Royal Melbourne Hospital, for the radiological studies necessary for this work, and to Dr. E. S. Finckh, for preparation and examination of the specimens of renal tissue obtained. The photographs and photomicrographs are the work of Mr. E. Matthaei, University of Melbourne, and Mr. R. Ingles, Clinical Photographer, Royal Melbourne Hospital.

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PULMONARY LESIONS IN RHEUMATOID ARTHRITIS[1]

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IT is now accepted that pathological changes in rheumatoid arthritis are not confined to the joints. Cardiac abnormalities such as pericardial adhesions, multiple myocardial foci resembling Aschoff bodies, and chronic valvular deformities of the "rheumatic" type are often present. Areas of necrosis resembling periarticular nodules in size and histological structure have been reported in the myocardium and valves (Baggenstoss and Rosenberg, 1944; Gruenwald, 1948).

Multiple small scars and mononuclear collections were found in the peripheral nerves (Freund *et alii*, 1942) and in the skeletal muscles (Steiner *et alii*, 1946; Gibson *et alii*, 1946). These are not histologically specific, but they are undoubtedly due to the "rheumatoid" process. In 1944, Rosenberg and his co-workers reported degeneration of the Malpighian bodies of the spleen; lymph node changes resembling amyloidosis; glomerulitis, and chronic interstitial nephritis. Fingerman and Andrus (1943) have referred to scleral lesions histologically resembling periarticular nodules.

References to pulmonary lesions are uncommon, although unexplained pleural adhesions were reported in 73% of all cases in which complete post-mortem reports had been published up to 1945 (Hench, 1948). In the same year Gruenwald encountered a case in which areas of necrosis, bounded by palisaded fibroblasts, were present in the pleura. Ellman and Ball (1948) recorded pulmonary lesions and obtained post-mortem material from two cases, in both of which chronic fibrosing pneumonitis and minute abscesses were present. In 1949, Yardumian and Kleinerman referred to the occurrence of pneumonitis, perivascular round-cell infiltration, and hyaline thickening and mononuclear infiltration of the walls of the alveoli.

Transient radiological abnormalities in the lung fields are not infrequent, but opportunities for pathological study of lung lesions are rare. The purpose of the present paper is to present the autopsy findings of three such cases. In one of these a large myocardial nodule with specific rheumatoid features was also present.

[1] Received on July 6, 1953.

CASE I

Clinical History

A man, aged fifty-seven years, was admitted to the Royal Melbourne Hospital on November 1, 1946. He had been in good health until 1934, and then, at the age of forty-five years, he had developed rheumatoid arthritis. At first the joint lesions progressed rapidly. Eighteen months after the onset of the disease, deformity of the interphalangeal joints of the fingers, and limitation of movement of the knees, elbows, wrists and shoulders were already severe. From 1943 until 1946 the disease had been stationary, and he was still able to walk, but he had noticed increasing pallor for several months. Six days before his present admission to hospital, he had rapidly developed shortness of breath, anorexia and œdema of the legs.

He was pale, and the lower part of the trunk was œdematous. The temperature was 38·3° C., the pulse rate was 112 per minute, and the respirations numbered 34 per minute. The apex of the area of cardiac dullness was 13·2 centimetres from the midline in the fifth left intercostal space. There was accentuation of the second sound at the aortic area. There were signs of fluid at the base of the right lung.

Inspection of the joints showed typical deformity, but no recent symptoms or signs were referable to them. Crepitations were present in both lungs. The liver was palpable three fingers' breadth below the right costal margin, and shifting dullness was present in the flanks. The blood pressure was 135 millimetres of mercury, systolic, and 95 millimetres, diastolic, and the urine contained a trace of albumin. The hæmoglobin value was 67%, and the white cells numbered 18,000 per cubic millimetre. The blood urea content was 30 milligrammes per 100 millilitres, the serum protein content was 6·7 grammes per 100 millilitres (albumin 3·7 grammes, globulin 3·2 grammes), and the result of the Van den Bergh test was three units of bilirubin, with a delayed direct reaction. The Wassermann test, the gonococcal complement fiaxtion test and the cephalin flocculation test all produced negative results. The electrocardiogram showed slurring of the *QRS* complexes in leads I and IV, flattening of the *T* wave in lead I, inversion of the *T* wave in lead IV, and upright *T* waves in leads II and III.

The patient's condition improved rapidly with rest in bed, limitation of fluid intake, and full doses of digitalis. Seven hundred and fifty millilitres of fluid, opalescent owing to the presence of polymorphonuclear and lymphocytic cells, were aspirated from the right pleural cavity. He became afebrile on the fourth day after his admission to hospital, and on the tenth day œdema and ascites had gone and the liver was of normal size.

He was readmitted to hospital thirteen months later, on December 2, 1948. He had been well until five weeks previously, when malaise, cough and progressive œdema had developed, with reduction of urinary volume.

On examination of the patient, œdema to the neck, ascites and bilateral pleural effusions were found. The

urine coagulated on being boiled, and its specific gravity was 1016. The cardio-vascular system was normal. Temperature, pulse rate, respiratory rate and blood pressure were normal.

The blood urea content was 52 milligrammes per 100 millilitres, the plasma protein concentration was 4·5 grammes *per centum* (albumin 3·3 grammes, globulin 1·2 grammes), and the ascitic fluid contained 600 milligrammes of protein per 100 millilitres, and numerous fat globules. An Addis count on 385 millilitres of urine revealed 12,000,000 red cells and

FIGURE I

Photograph of lung slices in Case I showing the pale foci of necrosis. Some of the necrotic material has been lost from one of the foci after the section was made.

314,000,000 pus and epithelial cells. The urine contained 1·2 grammes of protein *per centum*, 1·15 grammes being albumin and 0·05 gramme globulin.

Four days after the patient's admission to hospital, it was noted that œdema was increasing. The patient's weight was rising, and the urinary output remained low. The blood urea content was now 132 milligrammes per 100 millilitres, and the blood cholesterol content 305 milligrammes per 100 millilitres. There was a leucocytosis of 14,100 white cells per cubic millimetre due to neutrophilia with a slight "shift to the left" in the granular series. By December 29, 1948, the patient's blood urea content was 347 milligrammes per 100 millilitres, and death occurred on January 6, 1949.

Post-Mortem Findings

The autopsy was carried out fifteen hours after death. The body was wasted and œdematous. The fibrous pericardium was slightly thickened, and many fibrous band adhesions were present between the visceral and parietal layers. The intervening epicardium was congested. About 30 millilitres of fluid were present. The heart weighed 390 grammes and the muscle was red, soft and flabby. The endocardium and valves were normal. The aorta and larger coronary vessels were mildly atheromatous; the great arteries and veins of the thorax and abdomen were normal.

Each pleural sac contained about 100 millilitres of straw-coloured fluid. The pleura was milky white, but thin. Firm white subpleural nodules between two and three centimetres in diameter were present in the posterior part of the lungs (Figure I), two on the left side and three on the right. The overlying pleura was covered by a fine layer of fibrin. The largest nodule was situated in the middle lobe of the right lung, and had become softened to a pasty consistency except for a narrow peripheral rim. The necrotic tissue was not altogether structureless; bronchi vessels and fibrous septa were identifiable. Some of the lesions had a serpiginous edge, as though formed by the confluence of smaller foci. Small numbers of minute lesions of similar nature, measuring up to three millimetres in diameter, were also present. The intervening lung tissue was normal except for mild œdema.

The lymph nodes of the thorax and abdomen were discrete, slightly enlarged, soft, pink and œdematous. The spleen was large (520 grammes) and soft. The

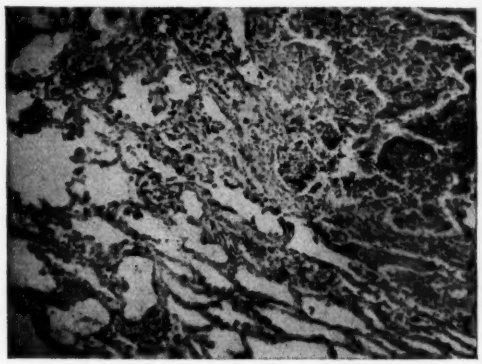

FIGURE II

Photomicrograph of the edge of one of the pulmonary necrotic foci in Case I. The alveoli are filled with fibrin and wandering cells and the septa have been destroyed. The adjacent lung shows thickening of the septa. (×40.)

capsule was not thickened. Several pale infarcts, the largest measuring seven millimetres by 10 millimetres, were present in the substance. The Malpighian bodies seemed unusually large.

Both kidneys were large and pale (the right weighed 570 grammes, the left 540 grammes). The capsules stripped readily, a pale, moist, smooth surface being left. The cut surface had a similar appearance, although the glomeruli were visible as red pin points. The interlobar and hilar veins on both sides contained laminated ante-mortem thrombus. The right renal vein was distended by thrombus as far as the inferior *vena cava*. The arteries of visible size appeared normal. The remainder of the examination gave negative findings.

Microscopic Findings.—Microscopic sections were stained with hæmatoxylin and eosin and with Masson's

trichrome stain. Staining by the Ziehl-Neelsen method for acid-fast organisms gave negative results. The nodular lesions in the lungs were spreading foci of fibrinous pneumonia (Figure II) undergoing central necrosis. The initial changes, as seen in the small patches, consisted of capillary congestion and infiltration of the septa by mononuclear cells and bars of fibrin. The alveoli were plugged by fibrin casts containing mononuclear cells. In larger patches central necrosis had developed, and the edge of the lesion appeared to be extending into unaffected lung tissue. This spreading edge was remarkably sharp, and the total width of the active zone intervening between normal lung and the central necrotic zone was seldom more than one or two alveoli thick. In some places the edge of the large lesions gave evidence of slower spread, as judged by the development of a narrow band of collagenous fibres, fibroblasts and large mononuclear cells. The necrotic material was largely granular débris of cytoplasmic and nuclear origin. Septa were not recognizable, but the swollen necrotic walls of small pulmonary vessels were still present. Polymorphonuclear cells were rare in the active zone, but had invaded some parts of the necrotic tissue.

In the pleura overlying the larger lesions mild fibrinous inflammation was seen. The predominant cell was the mononuclear macrophage, plasma cells were rare and polymorphonuclear cells were absent. In the walls of the small air passages and the adventitia of the pulmonary vessels was seen diffuse fibrosis with occasional foci of dense hyaline scar tissue.

The hilar and tracheo-bronchial nodes were highly vascular and cellular. A hyalinized rheumatoid nodule was identified in one section.

In the spleen, areas of infarction were present. Many of the small arteries showed severe inflammatory changes including fibrinoid change and necrosis.

In the kidneys the tubules were distended by homogeneous pale material or by cellular casts, and the epithelium was low or flattened. In the glomeruli "wire looping" was present. There was no crescent formation or wandering cell infiltration. The interstitial tissue was increased, and was heavily infiltrated by small round cells, plasma cells and polymorphonuclear leucocytes. In one section a three-zoned rheumatoid nodule with central necrosis was found in the adventitia of a patent interlobar vein. Many veins were blocked by recent thrombus. The adventitia of the interlobular arteries was infiltrated by wandering cells.

Many patches of fibrosis and occasional onion-skin scars were present in the myocardium. The muscle fibres were enlarged. The mitral ring and leaflets contained a large amount of dense collagenous tissue. All these lesions were old. Recent mild pericarditis was present as well as old fibrosis.

CASE II

Clinical History

The patient, aged sixty-seven years, was admitted to the Royal Melbourne Hospital on June 20, 1949. Six weeks before he had developed severe pain in the shoulders, elbows, wrists and knees. The pain wore off a little with activity; he continued his work for two weeks until his ankles became painful and swollen, but he could still walk in slippers. Two weeks prior to his admission to hospital he developed severe pain in the left side of the chest, from the shoulder across to the sternum. It was sharp and continuous, but was made worse by deep breathing. There was no dyspnœa. After five days the chest pain decreased, but the joints remained painful and swollen. There was a history of pneumonia nine years before. Two sisters had died of phthisis, but he had never had a cough.

The patient was dyspnœic and there was pitting œdema of the ankles. The left knee and the joints of both hands were swollen, hot and painful to move. His temperature was 38·3° C., the pulse rate was 120 per minute and the blood pressure 155 millimetres of mercury, systolic, and 75 millimetres, diastolic. The jugular venous pressure was raised, and the heart was enlarged to the left. The heart sounds were regular, a triple rhythm was audible in the mitral area, and a systolic bruit was present in the mitral and pulmonary areas. The percussion note and breath sounds were impaired at the bases of both lungs. The liver was enlarged and tender. The spleen and lymph nodes were not palpable. The electrocardiogram was normal. The hæmoglobin value was 11·6 grammes per 100 millilitres, the red cells numbered 5,020,000 per cubic millimetre, and the colour index was 0·82. There was a leucocytosis of 28,300 per cubic millimetre (neutrophile cells 61%, old metamyelocytes 16%, lymphocytes 17%, monocytes 2%). Platelets were numerous. No tubercle bacilli were found in the smear or culture from the sputum. Pleural fluid was examined four times. It contained lymphocytes and polymorphonuclear cells in moderate numbers and varying proportions on each occasion, and was sterile. No tubercle bacilli were grown. The blood uric acid content was 2·2 milligrammes per 100 millilitres. Radiological examination of the chest revealed moderate cardiac enlargement, pulmonary congestion, and collections of fluid at each lung base.

During the patient's first ten days in hospital venous congestion decreased and the joints became less swollen and painful. Fever persisted, and the fluid in the chest increased. Thereafter all signs became more severe, œdema recurred and the pulse became irregular. The patient died twenty days after his admission to hospital.

Post-Mortem Findings

The autopsy was carried out twelve hours after death. The body was well-nourished, with œdema of the legs and swelling of the right knee and wrist.

The visceral and parietal pericardial layers were slightly thickened, and recently-formed connective tissue totally obliterated the cavity. The heart weighed 410 grammes. The ventricular muscle was pale and soft. Fine strands of scar tissue were present in the wall of the left ventricle. The mural endocardium was normal. Examination of the mitral valve leaflets revealed fibrous thickening, and they were slightly nodular along the closure line. There was no commissural adhesion or reduction of the orifice. The aortic cusps were thickened and the adjacent surfaces of the right anterior cusp and the left cusps had fused. Examination of the coronary arteries revealed patchy intimal thickening, but the trunks and main branches were patent. The aorta and its major branches were moderately atheromatous. The great veins were normal.

A small pleural scar was present at the extreme apex on each side, and that on the right extended into the lung as a small mass of scar tissue pigmented with carbon. A local area of the lateral surface of the left lung was adherent to the chest wall by mature fibrous tissue. The lateral surfaces of the right lung and of the upper lobe of the left lung were adherent to the parietal pleura by strands of œdematous connective tissue, which had sealed off several loculi containing clear fluid. One loculus was filled by homogeneous white solid material. Strands of fibrous tissue were

present in all lobes, but were finer at the bases. The walls of the larger bronchi were thickened (Figure III).

The hilar and tracheo-bronchial nodes were much enlarged, soft, pink and œdematous. Examination of sections revealed numerous white foci up to two millimetres in diameter against the background of carbon pigmentation. The abdominal nodes were moderately enlarged, firm and pink. The spleen weighed 125 grammes. The capsule was normal, the Malpighian bodies were large, and two small pale subcapsular wedge-shaped infarcts were present.

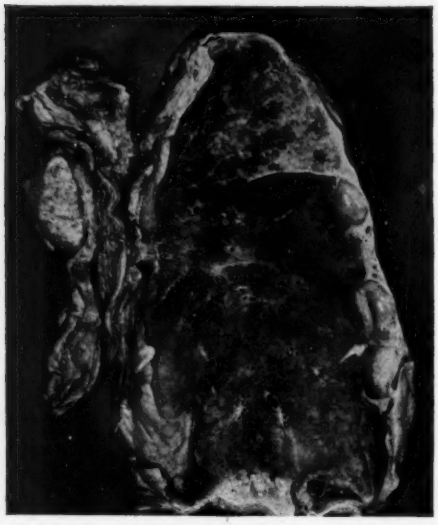

FIGURE III

Photograph of a lung slice in Case II. The pleura is thickened, and collections of fibrin and gelatinous fluid are loculated in the pleural space. The lung shows fine fibrosis, and the enlarged tracheo-bronchial lymph node is mottled with pale nodules.

The kidneys were of normal size (the right weighed 178 grammes and the left 165 grammes). The capsule stripped easily, a finely granular surface, mottled with red and pale areas about one millimetre in diameter being left. On section the cortex was mottled in the same way; it was of normal width. The medulla was normal. The smaller vessels were thickened. The knee joints were examined. The right contained a slight excess of synovial fluid; there was no congestion of the synovial membrane, but the periarticular tissues were œdematous. The remainder of the examination gave negative findings.

Microscopic Findings. — Fibrinous pleurisy of moderate grade was present (Figure IV). The pleura was loose, œdematous and infiltrated by wandering cells of all types; but there were no specific features. Polymorphonuclear leucocytes were present, but not in large numbers relative to other types.

The fine radiating fibrous strands observed macroscopically were found to be loose connective tissue varying greatly in cellularity and collagen content. Microscopic foci of fibrosis were numerous. The scars appeared to be growing actively; the inner part of each was less cellular with coarser collagen, whereas peripherally the collagen was fine, and small round cells and fibroblasts were numerous. At the spreading edge the septa became thickened and encroached on the alveolar spaces, and were gradually taken up in the scar. The septa contained large mononuclear cells, which often showed mitotic division or large multinucleate forms. Small round cells, fibroblasts and collagenous strands then appeared. Dilatation of capillaries was always present at the spreading edge.

In the centre of some of the scars the collagen bundles had become thick, tightly-packed, whorled and hyaline, and the cells had disappeared. Hæmosiderin pigment granules and peripheral aggregations of nuclear débris were occasionally to be seen. These changes were not confined to larger scars, although in general the smaller ones were less advanced.

There was a moderate degree of fibrosis of the bronchial walls and lymphoid tissue, and of the peribronchial connective tissue. The adventitiæ of the larger pulmonary arteries and all layers of the arteriolar walls were similarly affected.

In the lymph nodes the pale areas observed macroscopically proved to be hyaline nodules analogous to the pulmonary scars. Early lesions in lymphoid tissue consisted of focal thickenings of the reticulin fibrils of the pulp and lymph sinuses, and formed a network with the staining properties of collagen.

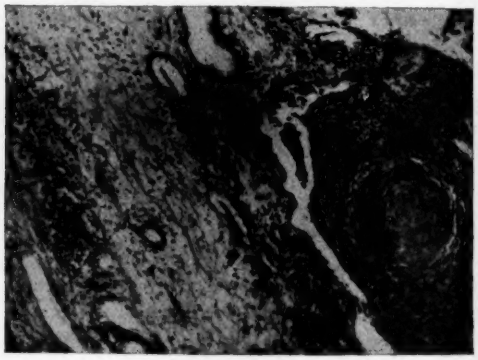

FIGURE IV

Photomicrograph of pleura in Case II, showing fibrinous inflammation and the formation of a small nodule. (×90.)

Numerous blood capillaries were present in these foci and hæmorrhages were frequent. The lymphocytes in the foci were decreased in numbers. Although fibroblasts never became numerous, the amount of collagen increased and thickening, whorling, fragmentation and hyalinization of the strands developed in the acellular core of the largest foci.

In the spleen, many nodular lesions resembling those in lymph nodes were present in the white pulp. They were independent of changes in the wall of the pulp artery. The nodule usually lay on one side of the artery, but sometimes partially or completely surrounded it. Even at this stage the wall of the vessel was often intact. Mild inflammation of the smaller arteries and arterioles was common. In some places, especially in the neighbourhood of areas of infarction,

"fibrinoid" change, necrosis and thrombosis were present.

The patchy myocardial scarring observed macroscopically was found to be due to islands of inactive fibrous tissue in the muscle bundles. Atrophic fibres sometimes survived in the scars, fibre hypertrophy was present elsewhere. These findings were considered to be due to ischæmia. However, a few active cellular Aschoff bodies, and small, dense, spindle-shaped scars were present in the adventitia of the small vessels.

Examination of the pericardium revealed diffuse recent inflammation of moderate grade, and also some areas of old fibrosis and perivascular round-cell infiltration.

The valves contained masses of poorly cellular collagenous tissue, but no evidence of recent change.

In the sections taken from the right knee joint, which was swollen at the time of death, the superficial layer of the synovial membrane showed diffuse polymorphonuclear infiltration, œdema and patches of fibrinous exudation. The capillaries and venules were widely dilated. Lymphocytic aggregations were present in the walls of the small vessels and in the perivascular connective tissue of the underlying ligamentous or fatty layer.

CASE III

Clinical History

The patient, an unmarried female, had been first admitted to the Prince Henry's Hospital on October 31, 1943, at the age of fifty-three years. She had suffered from rheumatoid arthritis of the hands and feet for thirty years, and from indolent ulcers of the legs for twenty-seven years. Over the preceding six years she had developed recurring attacks of pain, which had the characters of Raynaud's syndrome. Her presenting complaints were shortness of breath on exertion, and cough, with little whitish sputum, present for three months.

The patient was poorly nourished, and her arms and legs were wasted. In the fingers, wrists and toes advanced rheumatoid deformities were seen. The larger joints were not affected. There were small ulcers on the dorsum of the left foot and on the medial aspect of the left leg, which had been present for six years. The blood pressure was 210 millimetres of mercury, systolic, and 130 millimetres, diastolic. The jugular veins were distended to 2·5 centimetres above the level of the suprasternal notch, the apex beat was forceful and situated 10 centimetres from the mid-line in the fifth left intercostal space. The liver and spleen were not enlarged. The temperature was 37·7° C. The urine was free from sugar and albumin. The Mantoux and Wassermann tests failed to produce reactions, and the hæmoglobin value was normal. Radiological examination of the chest revealed gross cardiac enlargement to the right and left. The sharpness of the cardiac outline suggested fluid in the pericardium. The lung fields were clear except for shadows in the upper lobe of the left lung, which were interpreted as fibrosis.

Whilst the patient was in hospital the fever was intermittent, swinging as high as 38·3° C.; but aprexial intervals of a few days were common. An exacerbation of fever, venous congestion and arthritis occurred after eight weeks, but these gradually subsided and she was discharged from hospital fourteen weeks after her admission.

She was readmitted to hospital for eighteen weeks, six months later, with infected ulcers, massive cardiac œdema and arthritis of the right shoulder.

She was again readmitted to hospital two months later (February 22, 1945), with an impacted fracture of the neck of the right femur. She was discharged after fourteen months, able to get about, although the fracture had failed to unite, and the right knee and ankle were now stiff.

Six weeks later (October 17, 1946) she was again admitted to hospital, complaining of a severe stabbing pain in the upper part of the right side of the chest, and short attacks of severe coughing. She was very short of breath. The blood pressure was 245 millimetres of mercury, systolic, and 115 millimetres, diastolic. A friction rub was detected at the angle of the right scapula. Two weeks later the rub was still present, and radiological examination of the chest revealed a round, dense shadow six centimetres in diameter in the right upper zone.

Repeated examinations of the sputum for acid-fast organisms gave negative results, and there was no Mantoux reaction to one in 1000 old tuberculin.

Three weeks after her admission to hospital she developed pain in the back and exacerbation of fever, which persisted for four weeks. During the ensuing months she was rarely afebrile for more than a few days. The fingers became tense, glazed and swollen. Pressure sores appeared on the elbows and sacrum. The ulcer scars on the leg broke down. Attacks of vasospasm in legs were frequent, and a small patch of gangrene of the skin of one toe appeared. She became emaciated, and died on July 15, 1947.

Post-Mortem Findings

Adhesions were present throughout the pericardial sac, but were firmest on the front surface of the left ventricle near the apex. Here the myocardium was pale, opaque and thin. The heart was much enlarged, weighing 570 grammes. The anterior wall of the left ventricle and the septum were pale, and areas of yellow, firm, necrotic tissue were visible. The valves appeared normal. Mild atheroma of the aorta and coronary vessels was present.

Extensive connective tissue adhesions almost obliterated the left pleural sac, and covered the lateral surface of the upper lobe of the right lung except for the apex. A firm, rounded mass seven centimetres in diameter (Figure V) occupied the lower half of the upper lobe of the right lung. On examination of sections the mass was found to be composed of pale, rather dry, friable tissue, in which the remains of bronchi were identifiable. The mass was encapsulated by a layer of dense fibrous tissue, the inner edge of which merged into the necrotic material in some places, but elsewhere was sharply demarcated. The process had not crossed the interlobar fissure into the lower lobe. The upper part of the edge was slightly irregular, but expansion had been uniform in every other direction. The remainder of the lung was normal. Old pleural scars were present at the apices. The respiratory passages appeared normal.

There was a moderate degree of enlargement of the thoracic and abdominal lymph nodes, which were soft and pink. The spleen weighed 300 grammes. Patchy perisplenitis was present. The Malpighian bodies were large.

The alimentary canal and pancreas were normal. The liver weighed 1380 grammes, and focal fatty change and centrilobular congestion were present in it.

The suprarenals were rather small. The right kidney weighed 118 grammes, and showed mild arteriosclerotic change. The left kidney was small and granular, weighing 20 grammes. There were a narrow rim of cortex, small distorted pyramids and prominent

vessels. The ureters, bladder, uterus and adnexa were normal.

Microscopic Findings.—The structure of the massive lesion in the upper lobe of the right lung was indistinguishable from that of a subcutaneous periarticular nodule of rheumatoid arthritis (Figure VI). The inner and much the largest part of the mass consisted of matted bundles of coarse hyalinized collagen. Between this acellular core and the surrounding lung parenchyma there was a narrow zone containing many

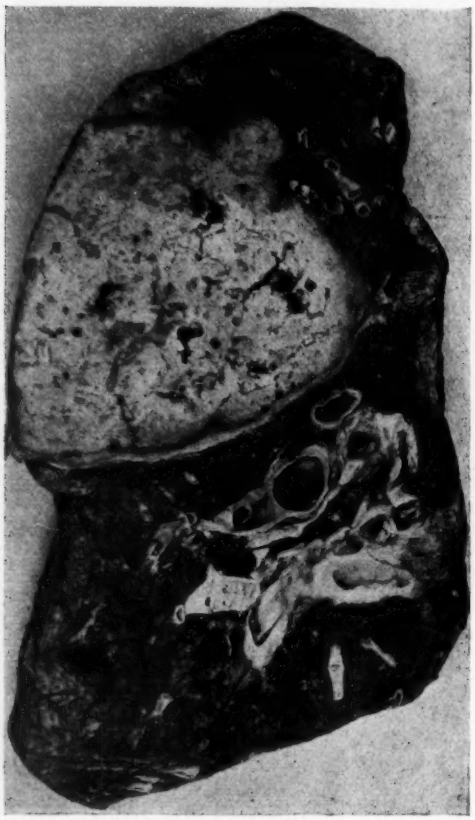

FIGURE V

Photograph of upper lobe of the lung in Case III, showing the large mass.

fibroblasts, a few small round cells and occasional areas of adipose tissue. The fibroblasts immediately adjacent to the inner zone were frequently orientated with their long axes at right angles to the serpiginous line of advancing hyalinization, the nuclei thus appearing palisaded. Giant cells of the foreign body type occurred in this region.

In some places polymorphonuclear invasion had broken up the hyaline collagen (Figure VII). This change was usually to be found near the margin of the central zone; the nearby fibroblastic zone was œdematous and contained many giant cells. After polymorphonuclear invasion the broken collagen reverted to a granular hyalinized state.

At the transition between the outer edge of the scar and pulmonary tissue, the alveolar septa were becoming thickened, and fibrin was present in the alveolar spaces.

The blood vessels in the outer fibrofatty zone showed thickening and fibrosis of all layers of their walls (Figure VIII); the innermost were completely occluded by organized thrombus. The remnants of such vessels were sometimes identifiable in the inner necrotic zone.

In addition to the main mass, loose fibrous and fibrofatty bands without necrosis were scattered through the lung tissue, and diffuse perivascular and peribronchial fibrosis was present. Chronic arteritis of the bronchial vessels and fibrosis of the intima of pulmonary veins were found. The hilar lymph nodes were largely replaced by a network of fibrofatty tissue, with islands of lymphocytes in the interstices.

FIGURE VI

Photomicrograph of the edge of the pulmonary nodule in Case III, showing the hyaline fibrous tissue (top) bounded by palisaded fibroblasts. (×200.)

The affected areas of myocardium were composed of necrotic muscle fibres which stained lightly and uniformly with eosin. There was only a slight increase of connective tissue between the fibres, and the arrangement of the fibres into bundles subdivided by septa was well preserved. Here and there disintegration into an amorphous granular state had occurred. Elsewhere there was invasion by wandering cells which had undergone nuclear fragmentation or pyknosis. The boundary zone between dead and living muscle was formed by a layer of loose cellular connective tissue completely devoid of muscle. The innermost fibroblasts were palisaded, and foreign-body giant cells and groups of mononuclear wandering cells were also present. The walls of the small vessels were thickened, owing to cellular infiltration, swelling of the internal elastic lamina, and intimal fibrosis.

DISCUSSION

Disseminated inflammatory lesions are regularly present in patients suffering from rheumatoid arthritis. The commonest extra-skeletal sites are the walls of the smaller blood

vessels, the heart (in which the pericardium, myocardium and valves are all susceptible), the areolar connective tissues, and the lymphoid and reticular tissues. In the lung, lesions occur in the pleura, the bronchi, the pulmonary and bronchial vessels and the alveolar walls.

Histological Features of the Lesions

The histological features of a particular lesion are determined by the extent, severity and speed of development of the inflammatory process.

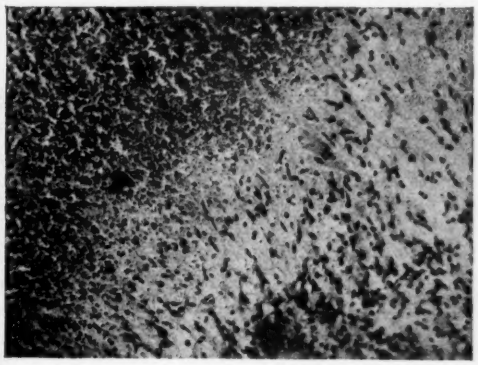

FIGURE VII

Photomicrograph of an area of the pulmonary nodule in Case III, in which polymorphonuclear leucocytes have invaded the hyaline material and then undergone pyknosis and fragmentation. (×150.)

There is great variation in the size of an area affected. The whole extent of a serous membrane may be uniformly involved, and in Case III a giant nodule reached a diameter of seven centimetres. At the other extreme, the lesion may be a focus of microscopic size.

Irrespective of extent, the intensity of the inflammatory process may be low or high. Small low-grade lesions occur in considerable numbers, especially in skeletal muscle.

In the milder lesions, there is no initial necrosis. A collection of mononuclear wandering cells develops and is gradually replaced by a tract of loose connective tissue, or by a packed mass of fibroblasts, or by a fibrous or fibro-fatty scar. Such scars are non-specific unless they contain more characteristic areas such as foci of gross collagen formation, hyalinization or necrosis with peripheral palisading of fibroblasts. Extensive low-grade changes account for the fibrous adhesions or milky opacities often found in the pleura or pericardium of subjects with chronic rheumatoid arthritis, and in all the present cases such lesions were present in the lungs and in the heart.

The severe grade of chronic lesion produces the typical "rheumatoid nodule". The core consists of a dense "scar" of interwoven collagenous bundles which undergo hyalinization. The cells become fewer and finally disappear. Secondary invasion by polymorphonuclear leucocytes may result in liquefaction of this material and the addition of much nuclear débris. The core is surrounded by a zone in which fibrosis is proceeding, and which contains large and small mononuclear wandering cells and numerous fibroblasts which may show a palisade arrangement.

In the lymph nodes and spleen the earliest changes appear in the sinus walls, which become progressively thicker and develop the staining properties of collagen. The amount of collagen

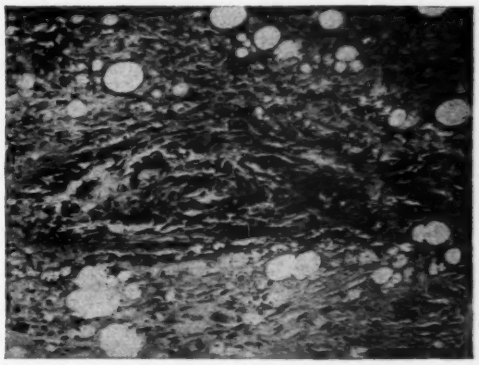

FIGURE VIII

Photomicrograph of the fibrous zone at the edge of the large pulmonary nodule in Case III, showing the destruction of a small artery and the development of adipose tissue in the scar. (×200.)

gradually increases, and a focal scar of tightly interlaced collagenous bundles is formed. This may ultimately develop the late changes of hyalinization, necrosis and liquefaction. The scar is surrounded by a zone of mononuclear wandering cells. In the white pulp of the spleen, the nodule may begin some distance away from the pulp artery, and may gradually extend around it until a complete ring is formed. The vessel may remain intact until a late stage unless it is independently affected. This lesion differs from the adventitial fibrosis of vessels in disseminated *lupus erythematosus*.

Early and Late Necrosis

In the severe type of acute lesion there may be initial necrosis of the affected tissue, which becomes permeated by fibrinoid and polymorphonuclear leucocytes, and surrounded by a mononuclear ring. Fibrinoid material, like fibrin in other inflammatory conditions, indicates acute damage to the capillaries of considerable severity; its significance is quantitative rather than qualitative. It is not common in rheumatoid disease except in the more rapidly progressive forms, and is not specific except in so far as the general pattern of distribution may be characteristic. In one of the present cases the pulmonary alveoli were plugged with fibrin casts.

No evidence was found that the ætiological agent exerts any effect on the preexisting collagen of an affected area which is not found in other inflammatory processes. Fragmentation of collagen in the early stage is present only in the more severe lesions, and is accompanied by severe damage to cells and to the other formed elements in the neighbourhood. In rheumatoid inflammation its presence is an index of the intensity and acuteness of tissue damage.

Late necrosis in a mass of rheumatoid scar tissue, as judged by gross hyalinization, disappearance of cells and certain secondary changes, should be distinguished from the early necrosis which occurs in a severe acute lesion. The secondary changes follow invasion by polymorphonuclear leucocytes. The hyaline collagen becomes broken up, the leucocytes undergo pyknosis or fragmentation. Liquefaction may occur with the production of a cystic space, or the débris may again become hyalinized to an amorphous granular material.

Late necrosis, such as that in the pulmonary and cardiac nodules in Case III, occurs only in older and larger lesions; thus it is the rule in the subcutaneous nodules, but is less common in visceral lesions, in which the requisite combination of size and severity is less frequent. It has been observed in cardiac nodules by Baggenstoss and Rosenberg (1944), and by Gruenwald (1948), in whose case it was present in the pleura and splenic capsule also.

In the outer layers of a nodule fibrous thickening of blood vessel walls and obstruction by organized thrombus are usually advanced. These changes must be important factors contributing to the central necrosis.

Palisading of the fibroblasts is well developed when necrosis of the central scar is occurring, and is found at the edge of the area of necrosis. The cause of palisading is not known. Multinucleated giant cells of the foreign body type are common near the line of necrosis. These cells differ in morphology and significance from the binucleate macrophages sometimes found in early lesions, such as those in the lung in Case I.

Lesion of Vessel Walls

The walls of blood vessels are more severely affected in rheumatoid arthritis than connective tissues elsewhere, and the small vessels, such as the small arteries, arterioles, capillaries, sinusoids and venules are more seriously affected than larger vessels. Considerable variation in the intensity of the inflammatory change may be observed in the case of the small arteries. This may range from mild fibrosis without blockage to fibrinoid infiltration or even complete necrosis of the wall and occlusion of the lumen by thrombus. The whole extent of the circumference may be involved, or only a segment—all layers, or one layer only. Infarction is only occasionally found, but this is not surprising, as the vessels affected are usually small. True infarcts may be differentiated from nodules by the absence of the characteristic peripheral zones, and by the grossness of the vascular lesions at the edge. Infarcts were found in the spleen in two of the present cases. The importance of ischæmia in producing late central necrosis in a large nodule has already been mentioned.

Examples in which capillary or sinusoidal injury is demonstrably the starting point of the process are to be found in the lymph nodes, in the renal glomerular changes and in the lesions of the pulmonary alveoli in Case I.

Sometimes a tract of connective tissue is manifestly affected although its small blood vessels are normal. In such examples capillary injury is probably an important factor; but it is not possible on histological grounds to determine whether it is the predominant factor.

Pulmonary Lesions

The lesions found in the lungs were as varied and widespread as those in other organs. They ranged from acute exudative foci to chronic scars of loose or dense texture. The pleura was probably the commonest site, but lesions were found in all parts of the lung—namely, parenchyma, vessels, bronchi and lymphoid tissue. The details may be summarized as follows: (*a*) Proliferation of mononuclear cells in the alveolar septa, with occasional binuclear forms, occurred in the early stages. (*b*) Sharply localized areas of

fibrinous pneumonia constituted a more severe grade of parenchymatous lesion. These showed capillary congestion, plugging of alveoli and alveolar ducts with fibrin, and polymorphonuclear infiltration. This might proceed to necrosis and softening or to organization. (*c*) Connective tissue " buds " resembling those described by Masson *et alii* (1937) and by Neubuerger *et alii* (1944) in rheumatic pneumonia were sometimes present. These consisted of minute nodules of connective tissue lying in alveolar ducts, budding from the wall. They were often covered by a single layer of cuboidal cells continuous with a similar layer lining the septa. Some buds arose as local thickenings of the alveolar wall due to low-grade fibrosis; others developed by organization of fibrin at the periphery of a larger focus. (*d*) Focal scars of variable density occurred in the pleura, alveolar walls, bronchi, vessels, and peribronchial and perivascular connective tissue. They ranged in size from minute connective tissue buds to a giant nodule seven centimetres in diameter structurally indistinguishable from the familiar subcutaneous nodule. Much of the fibrosis was non-specific, although such areas usually contained more advanced foci, recognizable as " rheumatoid nodules ". (*e*) Focal scarring or diffuse fibrosis was found in the walls of the smaller pulmonary vessels and of the bronchial arteries. (*f*) Acute fibrinous pleurisy and chronic pleural scarring occurred independently of or in association with other pulmonary changes.

CONCLUSION

In the active phases of rheumatoid disease, visceral lesions are consistently present and widespread in distribution.

In the chronic stage, active lesions may be found in many parts of the body even when the joint condition is quiescent. They probably appear in crops, and ultimately progress to inactive scars. Only the larger ones, or those active at the time of death, are recognizable at autopsy, whereas the articular deformities are always obvious even when active inflammation has died out. Hence radiological and even post-mortem observations underestimate the frequency of the extraarticular lesions, which are not rarities but an integral part of a generalized disease.

Inflammatory states, whether of organismal, physical or chemical origin, manifest a basic similarity modified only in detail by special factors peculiar to the exciting cause (King, 1948). The present cases illustrate the main characteristics of rheumatoid inflammation. It is disseminated, focal, non-suppurative, persistent and prone to result in dense hyaline scars which may undergo secondary changes. Its special characters are the consequences of such factors as the intensity, extent, duration and localization of the action of the inflammatory process rather than of any unique attribute of the tissue reaction.

SUMMARY

Clinical and autopsy studies on three patients with rheumatoid arthritis are reported. Rheumatoid arthritis had been present for fifteen years, six weeks and thirty-five years respectively. Cardiac failure and symptoms of respiratory disease were present in each.

The pathological changes in lungs, heart, lymphatic tissues, connective tissues and blood vessels were qualitatively similar to the typical rheumatoid nodule, but varied widely in severity and extent. They represent a non-specific inflammatory response to the ætiological agent.

It is concluded that visceral lesions are to be found in the chronic as well as in the acute phases of the disease with a frequency which justifies their acceptance as an integral part of the disease.

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THE EFFECT OF "PRISCOL" IN PULMONARY HYPERTENSION[1]

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PULMONARY hypertension may be the outcome of a number of factors affecting the pulmonary circulation. Pulmonary artery pressure may be elevated by the rise in left auricular pressure occurring in left ventricular failure or in mitral stenosis. It may be raised when the rate of pulmonary blood flow is abnormally increased. Cournand (1950) found in normal subjects that with increasing pulmonary flow the pulmonary artery pressure did not rise until the rate of flow reached about three times normal; thereafter the pressure began to rise progressively. Finally, pulmonary artery pressure may be raised because of increased pulmonary vascular resistance, the result of functional or of organic changes, or of both.

Effective relief of pulmonary hypertension in a particular case depends upon an accurate assessment of the responsible factors and our ability to treat them. When raised left auricular pressure is the cause, the relief of left ventricular failure, or of the mechanical obstruction of mitral stenosis, may cause pulmonary pressures to return to normal. Increase in pulmonary blood flow due to a left-to-right shunt may be cured surgically. Ligation of a patent *ductus arteriosus* has been carried out for a number of years; techniques for the repair of auricular and ventricular septal defects are now being developed (Gross *et alii*, 1952; Bailey *et alii*, 1952) and may soon become established procedures.

Increased pulmonary vascular resistance poses a more difficult therapeutic problem. It is a factor in all cases of severe pulmonary hypertension, whether as sole cause, as in primary pulmonary hypertension, or complicating one of the other major causes mentioned above. Thus it may be superimposed upon back-pressure from the left auricle, as in the severe pulmonary hypertension of mitral stenosis, in which the rise of pressure in the pulmonary artery is out of proportion to that in the left auricle. On the other hand, it may complicate increased pulmonary blood flow, as in those less common cases of congenital left-to-right shunt in which pulmonary pressures, at an early or late stage, rise to systemic levels, with reversal of the shunt and consequent cyanosis—the so-called Eisenmenger syndrome.

The increased resistance may be due to organic obstruction of the small pulmonary vessels, as in repeated pulmonary embolism, in occasional cases of lymphangitic carcinomatosis, or in cases of pulmonary arteritis, including bilharzial *cor pulmonale*. On the other hand, there is evidence that it may be largely, if not wholly, functional. In emphysema it is now well established that functional factors play a considerable part in the production of high pulmonary pressures. Patients who show severe pulmonary hypertension in the acute phase of pulmonary heart failure may show normal or nearly normal levels after recovery (Mounsey *et alii*, 1952). Here anoxia appears to play a major part as the hypertensive agent (Motley *et alii*, 1947), possibly linked with hypercapnia (Yu *et alii*, 1953).

Although many subjects of primary pulmonary hypertension show obstructive vascular lesions, in a number at autopsy no significant organic changes have been found (Dresdale *et alii*, 1951; McKeown, 1952). It is possible that in others the vascular changes are the end-results of what was originally a functional condition. This has a parallel in essential hypertension, in which it appears that arteriolar constriction may occur years before the changes of diffuse hyperplastic sclerosis appear in the small vessels (Castleman and Smithwick, 1943). In mitral stenosis, too, in a significant proportion of subjects who have died from their disease, no pulmonary vessel changes are found. In many of the more severe cases there is medial hypertrophy in the pulmonary arterioles and often in the small arteries, but this again may be a compensatory or secondary change following initial functional constriction, and in many cases may prove reversible after valvotomy. Actual sclerotic lesions have been

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found to be no more common than those seen normally in older people without evidence of raised pulmonary pressures (Henry, 1952).

Except in cases of anoxia, the cause of functional increase in pulmonary arteriolar resistance is unknown, just as the cause of the increased systemic peripheral resistance which raises blood pressure in essential hypertension is unknown. If indeed it is primarily functional, it should, in the early stages at least, be reversible. The finding of a drug which could lessen or abolish it would offer the physician a line of treatment in cases in which at present he feels singularly helpless. Such a drug might prove effective therapy in at least a proportion of cases of primary pulmonary hypertension, a disease at present uniformly fatal. It would be of value in the treatment of patients with mitral stenosis, in whom pulmonary hypertension persists after a technically successful mitral valvotomy. Finally, it might be indicated in certain cases of the Eisenmenger syndrome, in which pulmonary hypertension sufficient to reverse a shunt through a septal defect or patent ductus has developed and is apparently progressive, with increasing cyanosis. In this type of case operation to close the abnormal communication is at present considered to be contraindicated, because it does not deal with the increased pulmonary resistance (Dammann *et alii*, 1953). If an effective drug was available to lower pulmonary resistance and abolish cyanosis, surgical treatment could then be carried out.

With these considerations in mind, an attempt has been made to measure the effect of "Priscol" (2-benzyl-imidazoline) on the pulmonary circulation in eight cases of pulmonary hypertension of varying ætiology. The trial of this drug was suggested by a report by Dresdale *et alii* (1951) of its use in two cases of primary pulmonary hypertension, in which a considerable fall of pulmonary artery pressure and pulmonary resistance occurred after injection at cardiac catheterization.

Material and Methods

The eight patients studied comprised two with mitral stenosis and considerable pulmonary hypertension, two with anoxic *cor pulmonale*, two with pulmonary hypertension occurring in congenital heart disease, and finally two believed to be suffering from primary pulmonary hypertension. This diagnosis has been substantiated subsequently in one case (Case VII) at autopsy (Clarke and Tait Smith, 1953).

The day prior to catheterization a trial dose of "Priscol" was given under resting conditions, to gauge the subject's reaction to the drug and to allow observation of its effect on pulse and systemic blood pressure.

Cardiac catheterization was carried out with the patient in the resting post-absorptive state. Mean pulmonary artery pressures were measured by saline manometer in three cases, and by a capacitance electromanometer (Hansen, 1949) in the remainder. Pulmonary blood flows were calculated by the Fick principle, mixed venous blood being obtained from the main pulmonary artery, and arterial blood by femoral artery puncture; in Case III, an example of the Eisenmenger syndrome with right-left shunt, the oxygen saturation of the left auricular blood was assumed to be 97·5%. Oxygen consumption was calculated from analysis of expired air collected in a Douglas bag and analysed for oxygen and carbon dioxide content in the Haldane gas analysis apparatus.

After resting pulmonary artery pressures and pulmonary blood flow had been measured, "Priscol" in dosage appropriate to the case was injected through the catheter into the main pulmonary artery. Further pressure readings were taken, and the pulmonary blood flow was again estimated from three to four minutes after injection.

Total pulmonary resistances were calculated according to the formula

$$TPR = \frac{PAm \times 1332}{Qpa}$$

where TPR=Total pulmonary resistance in dynes/sec/cm^{-5}.

PAm=Mean pulmonary artery pressure in millimetres of mercury above the sternal angle.

Qpa=Pulmonary blood flow in millilitres per second.

Results

Table I summarizes the results.

The dose of "Priscol" used in the earlier cases was cautious, and probably too small for full effect. It had produced flushing at the first injection, but did not do so to the same extent at catheterization.

The effect of the drug on systemic blood pressure, determined by the cuff method at the trial injection, was slight, a rise being recorded in five cases and a slight fall in three. This is in keeping with the observations of others (Wakim *et alii*, 1950; Rottenstein *et alii*, 1951).

TABLE I

Summary of Results

Case	Diagnosis	Dose of "Priscol" (Milligrammes)	Systemic Blood Pressure. (Millimetres of Mercury)[1]		Mean Pulmonary Arterial Pressure. (Millimetres of Mercury)		Pulmonary Flow. (Litres per Minute)		Total Pulmonary Resistance. (Dynes/sec/cm^{-5})		
			Before	After	Before	After	Before	After	Before	After	Change
I	*Cor pulmonale*	10	114/84	112/72	36	30	5·75	5·8	500	414	−17%
II	Mitral stenosis	10	148/104	156/108	74	60	2·2	2·45	2486	1957	−21%
III	Eisenmenger syndrome ..	10	98/86	112/88	77	76	2·0	2·9	3077	2094	−33%
IV	Aorto-pulmonary septal defect	25	140/90	150/96	82·5	78	—	—	—	—	—
V	Mitral stenosis	10	125/70	115/68	66	78	2·76	3·02	1911	2258	+18%
VI	*Cor pulmonale*	20	100/80	110/78	65	56	1·92	3·84	2699	1165	−57%
VII	Primary pulmonary hypertension	25	114/86	114/82	48	34·5	2·72	3·85	1410	716	−49%
VIII	Primary pulmonary hypertension	50	134/86	138/90	47	46	3·53	5·85	1064	628	−41%

[1] Systolic/diastolic.

In six of the eight cases a fall in the total pulmonary resistance was observed; in another it could not be measured satisfactorily; while in one case (Case V, mitral stenosis) there was a rise. The total pulmonary resistance includes not only the resistance across the arterioles, but also that across the mitral valve. In the six subjects without mitral stenosis the latter could reasonably be assumed to be normal (resting pulmonary capillary pressures were normal in the two cases in which it was measured, Cases VII and VIII). Thus in these cases a fall in total pulmonary resistance would reflect a fall in pulmonary arteriolar resistance.

In mitral stenosis, however, the resistance at the mitral valve may make up a considerable part of the total pulmonary resistance. With rising flow, this resistance will not fall. Hence the considerable fall of total pulmonary resistance in Case II must have been largely if not entirely due to a fall in arteriolar resistance. On the other hand, in Case V the rise in pulmonary artery pressure and total pulmonary resistance may have been contributed to partly or largely by a rise in pressure in the left auricle as blood flow was increased. Thus it becomes uncertain in this case what effect "Priscol" had on the pulmonary arteriolar resistance.

DISCUSSION

This paper presents briefly the results of an attempt to measure the effectiveness of "Priscol" in lowering increased pulmonary vascular resistance. "Priscol" has been found to have sympatholytic and adrenolytic properties (Chess and Yonkman, 1946), and may have a direct action on vessels. It was chosen partly because of the report of its use mentioned earlier, and partly because it has been found to have little or no effect on general systemic peripheral resistance, its action being mainly on skin vessels in the extremities. Hence it affects the systemic blood pressure little if at all. It tends to raise cardiac output slightly (Rottenstein *et alii*, 1951). These features of the action of "Priscol" contrast with those of the methonium group of drugs, which have a powerful action on the systemic circuit. If, in a case of primary pulmonary hypertension, the systemic action was relatively more powerful than that on the pulmonary circuit, the effect of the drug might be deleterious rather than helpful; hypotensive reactions might be profound, for the heart would be unable to compensate for the falling systemic pressure by increasing pulmonary flow. Moreover, the development of tolerance is often a feature of the continued use of these drugs; in the pulmonary circulation, where objective measurement cannot be frequently repeated and the effect of the drug checked, this would be a considerable disadvantage. On the other hand, subjective effects of "Priscol" such as flushing are sufficiently apparent to the patient to give an indirect indication of adequate dosage.

The results indicate that, under the conditions of an acute experiment, "Priscol" given into the blood stream may lower pulmonary peripheral resistance. This presumably comes about by relaxation of the pulmonary arterioles, with dilatation of existing vessels and possibly opening up of new channels. In most of the

cases the pulmonary flow rose to some degree, and it may be argued that pulmonary relaxation with rise of flow is a normal phenomenon. This is indeed true at normal pressures and low levels of resistance; it tends to prevent a rise of pulmonary artery pressure with rising output (Riley *et alii*, 1948). But in the cases under discussion, with high pulmonary resistances, it is well known that a small increase in pulmonary flow, for instance that occurring on mild effort, will produce a steep rise of pulmonary artery pressure. At the same time the resistance, rather than falling, remains the same or even increases (Werko and Eliasch, 1952; Howarth and Lowe, 1953). The pulmonary arterioles appear to have lost their normal property of relaxation with rise of flow. It may be that "Priscol" can restore this to some extent.

It has also been suggested that the systemic peripheral effects of the drug may sequestrate a certain volume of blood, so that the pulmonary arterial system is temporarily depleted. Unfortunately we have as yet no accurate method of measuring the volume of the pulmonary vessels in life. The cardiopulmonary blood volume (Ebert *et alii*, 1949) gives some indication of the total volume of the pulmonary vascular bed, but not of the proportion contained on the arterial side. Now it may be that the pulmonary artery is less full when the pressure in it drops, but the fact that pulmonary flow rises rather than falls seems to indicate that, if there is a decrease of volume, it occurs not because less blood enters the pulmonary artery but because more leaves it. This could be due to increased pulmonary flow through relaxed arterioles.

In most of the cases under trial, treatment with "Priscol" was not considered indicated therapy. Thus, in the cases of *cor pulmonale* adequate oxygenation was the prime necessity. In mitral stenosis, valvotomy was the treatment of choice, and subsequently was carried out with success. In the congenital cases, one was that class of the Eisenmenger syndrome which produces cyanosis from early life and is not progressive, and in which pulmonary vasodilatation would seem contraindicated; in the other, a large left-to-right shunt was largely responsible for the hypertension, and its repair was the obvious remedy. Unfortunately, although the shunt was aorto-pulmonary, at thoracotomy the patient was found to have not a patent *ductus arteriosus*, as had been hoped, but an aorto-pulmonary septal defect, a lesion at present not amenable to repair.

It was in the two cases of primary pulmonary hypertension that some means of pulmonary vasodilatation was held to be urgently indicated; in fact, it seemed the only therapy possible. Sympathectomy has been suggested (Dresdale *et alii*, 1951), but has not been reported as having been carried out; Werko and Eliasch (1952) found a rise rather than a fall of pulmonary pressures after a bilateral stellate ganglion block. Hence, after catheterization a trial of treatment with "Priscol" given by mouth was commenced.

The patient in Case VII, who was in cardiac failure shortly before investigation, left hospital improved, but about three months afterwards slipped back into congestive failure. On her recovery she was given hexamethonium bromide by mouth, 250 milligrammes three times a day. This produced no untoward reactions, and indeed it appeared to improve her exercise tolerance. She died some three months later in an epileptiform convulsion. Autopsy revealed pronounced right ventricular hypertrophy, with intimal thickening and medial hypertrophy in the small pulmonary vessels.

In view of the foregoing observations, it was decided in Case VIII to test not only "Priscol", but also the ganglionic blocking agent hexamethonium, and "Regitine", a sympatholytic agent. Hexamethonium produced a slightly greater lowering in pulmonary vascular resistance; "Regitine" was not quite so effective. However, as hexamethonium given by mouth produced severe postural hypotensive reactions, with one unexplained breathless attack, it had to be abandoned. Subsequently the patient was placed on a maintenance dose of "Priscol" by mouth, 75 milligrammes five times daily, sufficient to give her an appreciable flush. She has remained on this dose for four months. She has had symptomatic improvement and feels she can do more, but objectively there is as yet no definite change. She continues under observation.

SUMMARY

In an attempt to assess its effectiveness in lowering increased pulmonary vascular resistance, "Priscol" (10 to 50 milligrammes) was injected into the pulmonary artery at cardiac catheterization in eight patients with pulmonary hypertension of varying ætiology. A fall in the total pulmonary resistance was observed in six of the seven cases in which it could be measured. This was thought to be due to pulmonary vascular relaxation.

In two cases of primary pulmonary hypertension, in both of which there was a considerable fall of total pulmonary resistance after the injection, the administration of "Priscol" by mouth was commenced. One patient has since died; the other, objectively unchanged although symptomatically improved, is under observation.

The need is stressed for a drug which will lower increased pulmonary vascular resistance when this is functional. Possible uses of such a drug are discussed.

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DISSEMINATED LUPUS ERYTHEMATOSUS[1]: A CLINICO-PATHOLOGICAL REVIEW OF SEVEN CASES

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WITH the concept of a disease process involving the collagen supporting tissues of the body and the discovery of a specific diagnostic cellular reaction in the bone marrow and peripheral blood, the recognition of disseminated *lupus erythematosus* has been considerably simplified. During the past three years seven patients suffering from the disease have been admitted to the wards of the Royal Adelaide Hospital, and of these five have died. All cases have been proved at autopsy or by the finding of the characteristic L.E. cell or both. It is proposed to discuss and attempt to correlate the clinical and pathological aspects of disseminated *lupus erythematosus* with reference to these cases.

HISTORICAL SURVEY

As a localized lesion of the skin, *lupus erythematosus* was first described by Hebra in 1845, and it was given its present name by Cazenave in 1851 because of its supposed association with cutaneous tuberculosis. In 1872 Kaposi directed attention to the possibility of a disseminated form of the disease, and Osler, in a series of essays between 1895 and 1903, delineated a clinical picture of the condition, stressing the generalized nature of the symptoms and signs. He emphasized the presence of endocarditis and of purpura and hæmolytic anæmia, and the frequent occurrence of abdominal pain. He stated that the disease could occur without the typical lesions of the skin. Some of his cases would not be accepted today as proven examples of disseminated *lupus erythematosus*, but the fundamental observations that he made are unaltered.

In 1924 Libman and Sacks described four cases of an atypical, non-bacterial, verrucous endocarditis and related them to disseminated *lupus erythematosus*. They also noted the lesions in the spleen. Baehr *et alii* (1935) described the " wire loop " and other characteristic changes in the kidney, and the morphological appearances were integrated by the detailed study of Klemperer *et alii* in 1941. From these observations arose the concept of disseminated *lupus erythematosus* as a widespread disease affecting the collagen connective tissues of the body and resulting in a type of degeneration which has been likened to the fibrinoid change described by Neumann in 1896. Since that time varying degrees of this connective tissue change have been observed in scleroderma, dermatomyositis, *polyarteritis nodosa*, rheumatic fever and rheumatoid arthritis—a group of conditions which Klemperer, Pollack and Baehr (1942) have tentatively called the collagen diseases.

The collections of hæmatoxylin-staining bodies, devoid of regular nuclei and cellular structure, were first observed in the cardiac valvular vegetations by Gross in 1932. Ginzler and Fox in 1940 described similar large hæmatoxylin-staining aggregates in necrotic lymph nodes in this disease, and Klemperer *et alii* (1950), by histochemical methods, have identified the material as depolymerized desoxyribosenucleic acid and related it structurally to the inclusion bodies of the L.E. cell.

After the original descriptions, the greatest clinical advance has been the discovery of a specific phagocytic cell in the bone marrow and peripheral blood of patients suffering from disseminated *lupus erythematosus* (Hargraves, Richmond and Morton, 1948). This has considerably broadened the clinical aspects of the condition, and permitted diagnosis in many cases which would formerly have gone unrecognized because of the early bizarre and seemingly unrelated manifestations of the disease.

ÆTIOLOGY

In the ten years preceding the admission of the first of these patients to hospital, disseminated *lupus erythematosus* had been diagnosed only twice in the Royal Adelaide Hospital. The sudden rise to seven cases in three years must be ascribed, to some extent, to an increasing awareness of the disease entity and to the improved methods of establishing the diagnosis; nevertheless there would appear to be a real increase in the frequency of occurrence (Lian *et alii*, 1947). Dubois (1952) states that

[1] Received on September 14, 1953.

in his hospital the diagnosis is confirmed as frequently as that of pernicious anæmia, and in a more recent communication (Dubois, 1953) that the disease occurs half as frequently as acute rheumatic fever. It has been suggested by a number of authors that this increase parallels the introduction and frequent use of the sulphonamide preparations and penicillin (Gold, 1951), although attempts to relate the onset and exacerbations of the disease to these substances have yielded inconclusive results (Jessar *et alii*, 1953). Certainly, in the clinically and pathologically related condition of *polyarteritis nodosa*, a direct relationship with drug sensitivity can be established; but in *lupus erythematosus* the association is more tenuous, and the well-known tendency to spontaneous remissions and relapses makes it extremely difficult to evaluate the adverse effect of therapeutic substances. Walshe and Zimmerman (1953) may have provided a link by their finding of typical L.E. cells in the blood of three patients suffering from severe hypersensitivity reactions to penicillin.

Earlier reports of the disease stressed the frequency of pulmonary tuberculosis at autopsy, and ascribed many of the manifestations of tissue catabolism to this finding. Few observers today would agree that tuberculosis is related to *lupus erythematosus*, except in the role of a secondary invader. The real ætiology of the disease is unknown. There is general agreement that the clinical and pathological changes are due to a "fibrinoid" degeneration of collagen throughout the body, but the cause of this reaction and its specificity are undetermined (Klemperer, 1950). There is a case for the lesions being of allergic nature, for they have been reproduced both experimentally and in the human being by illnesses which are induced by antigen-antibody reactions (Rich, 1946; Fox, 1943). Teilum (1946 and 1948) believes that the fibrinoid change is produced in this manner, and that the hyperglobulinæmia, the periarterial fibrosis of the spleen, and the "wire-loop" lesion of the glomerulus are all a reflection of a primary allergic hyperglobulinosis in the reticuloendothelial system. He likens these changes to those observed in primary atypical amyloidosis and Boeck's sarcoidosis. Moolten *et alii* (1953) have recently isolated the virus of Newcastle disease from the red cells of a patient presenting with *lupus erythematosus*, and claim to have reproduced the L.E. phenomenon *in vitro* with this virus. No other specific organism has been isolated, although the hæmolytic streptococcus has been suggested as a possible cause (Barber, 1941).

In general, the outstanding tendency for the disease to affect women of the child-bearing age and its uniformly fatal outcome preserve its clinical identity.

In the present series no definite ætiological factor was apparent. All the patients were women, and all except one (Case I) were within the reproductive period of life. Sulphonamides had been administered in several instances, but it was impossible to judge whether this was before or after dissemination of the lesions had occurred, or whether the drug itself or the natural history of the disease was responsible for the advancing clinical signs. Sensitivity to sunlight was not a feature in any of the patients.

Case I was of interest from an ætiological point of view, since the patient's chronic discoid rash had been present for twenty-five years before dissemination of the lesions occurred.

CASE I.—S.W., a married housewife, aged fifty-eight years, was admitted to hospital on December 26, 1951. She had borne a chronic, scaling erythematous rash over her face, her neck and the upper part of her chest for twenty-five years. For nine months prior to her admission to hospital she had suffered from arthritis of the fingers and knees of mild degree. Three months before her admission she had developed a severe respiratory infection, which had confined her to bed for three weeks and left her with a chronic non-productive cough, anorexia, exertional dyspnœa and extreme weakness. There was no record of the type of treatment she had received for this illness. Her symptoms persisted until a fortnight before her admission to hospital, when she became acutely ill with a high temperature, sweating, pain across the front of the chest, and an increase in the intensity and extent of the chronic skin rash. There was no history of unusual exposure to light. The menopause had occurred at the age of fifty-five years. There were no previous illnesses.

The patient was a flushed, elderly woman in acute respiratory distress, with an erythemato-macular rash, desquamating at the edges, and involving the face, the neck and the anterior chest wall. The temperature was 102·8° F., the pulse rate 96 per minute and regular, and the respirations numbered 28 per minute. The heart was not enlarged on clinical examination. There was a soft apical systolic murmur. Signs of consolidation were present at the base of the left lung, with scattered inspiratory rales over both lung fields. The remainder of the examination gave normal findings.

The results of laboratory investigations were as follows: the hæmoglobin value was 10·3 grammes *per centum* (68%); the red blood cells numbered 3,900,000 per cubic millimetre; of the leucocytes, 41% were polymorphonuclear leucocytes, 50% lymphocytes, 7% monocytes and 1% eosinophile cells; an occasional myelocyte was seen. An X-ray examination of the chest revealed two old calcified tuberculous lesions, but no evidence of active inflammation.

Her temperature continued to range between 100° and 103° F., and she complained of severe intermittent lateral and retrosternal chest pain. Shortly after her admission to hospital extensive ulcerative stomatitis

developed, which was followed by perianal and vaginal ulceration. The liver and spleen became palpable. *Lupus erythematosus* cells were observed in the peripheral blood on January 26, 1952, and on several subsequent occasions. Despite massive penicillin therapy the clinical signs in the lungs progressed, and she died in acute respiratory distress on February 7.

At autopsy an extensive rash was present on the face, neck, chest, arms, forearms and shins. Moderate enlargement of the heart was present, but no endocarditis. There was bilateral bronchopneumonia with pleural adhesions. The cause of death was bronchopneumonia.

In this case chronic discoid *lupus erythematosus* became disseminated about nine months before the patient's death. There was no obvious reason for the sudden extension of the disease. Mild initial arthritis was present, but the symptoms and signs were predominantly those of respiratory involvement, and in the early acute phase the symptoms were out of proportion to the physical signs.

This case supports the general impression that chronic discoid *lupus erythematosus*, the subacute form and the acute disseminated type are all gradations of the same disease. In the large series of Montgomery and McCreight (1949, one-third of the acute cases had commenced as chronic lupus.

CLINICAL FEATURES

The more prominent symptoms and physical signs at onset are shown in Tables I and II. Evidence of increased tissue catabolism was present in all cases, and included fever, weight loss, weakness and anorexia. The patients were all acutely ill, but the rapidity of onset of the illness varied from a few days in Case VII to eight months in Case III. Only in Case II did the temperature fluctuations show any periodicity, the temperature being elevated for two or three days in every ten. The significance of this finding is doubtful, since the patient was receiving a number of different treatments over this period of time.

Arthritis

Arthralgia and arthritis were present in all cases. Except for Case I, the onset preceded the appearance of the rash by periods varying from one week to nine months. This sequence is relatively common (Friedmann *et alii*, 1953). Joint manifestations ranged from transient attacks of swelling and pain to severe polyarthritis with deformity. They led to an initial diagnosis of acute rhemuatoid arthritis in Case VII and to the suspicion of acute rheumatic fever in Case II. There is no characteristic clinical appearance, and the arthritis may involve a single joint or affect many. Effusions were present in two cases. Friedmann *et alii* (1953) classify the articular manifestations into three main types: firstly, myalgias and arthralgias; secondly, acute and subacute migratory polyarthritides; and thirdly, chronic progressive polyarthritides with deformity. Slocumb (1940) states that the joint pains respond to salicylate therapy, but the fever persists. Salicylates afforded no relief from joint pain in three of these cases, and it is considered that the negative response is suggestive of the arthropathy of *lupus erythematosus*.

The following two cases demonstrate the diversity of the joint manifestations.

CASE II.—R.T., an unmarried salesgirl, aged fifteen years, was admitted to hospital on February 21, 1953. Six weeks previously she had suffered a slight sore throat, which had kept her in bed for one day. Four weeks later her right knee and left ankle had become swollen and painful, but had returned to normal within two days. A week before her admission to hospital she noticed a rash on the cheeks, nose and forehead, accompanied by frequent headache. On the evening before her admission to hospital swelling and pain recurred in the ankle and both elbows.

TABLE I
Frequency of Symptoms

Symptoms	Case Number							Total
	I	II	III	IV	V	VI	VII	
Cough	+	+	+	+	+	+	+	7
Chest pain	+	+	−	+	+	+	+	6
Arthralgia	+	+	+	+	−	+	+	6
Anorexia	+	−	+	+	+	+	+	6
Weakness	+	−	+	+	+	+	−	5
Weight loss	+	−	+	+	+	+	−	5
Œdema	−	−	+	+	−	+	+	4
Dyspnœa	+	−	−	+	−	+	+	4
Nausea and vomiting	−	−	+	+	−	−	+	3
Neurological symptoms	−	−	−	+	+	−	+	3
Headache	−	+	−	−	−	+	−	2
Photophobia	+	−	−	−	+	−	−	2
Abdominal pain	−	−	−	+	−	−	+	2
Menstrual disorders	−	−	−	−	−	+	−	1

TABLE II
Frequency of Signs

Symptoms	Case Number							Total
	I	II	III	IV	V	VI	VII	
Fever	+	+	+	+	+	+	+	7
Rash	+	+	+	+	+	+	+	7
Systolic murmur	+	+	+	+	+	+	+	7
Arthritis	+	+	+	+	−	+	+	6
Enlarged heart	−	+	+	+	+	+	+	6
Pleural effusion	+	+	+	+	−	+	+	6
Stomatitis	+	+	−	+	+	+	+	6
Lymphadenopathy	−	+	−	+	+	+	+	5
Pericardial friction	−	+	−	+	+	+	+	5
Respiratory infection	+	+	+	−	−	+	+	5
Hepatomegaly	+	−	+	+	−	+	−	4
Convulsions	−	+	−	+	−	−	+	3
Splenomegaly	−	−	−	+	−	+	−	2
Purpura	−	+	−	−	−	+	−	2
Meningismus	−	−	−	−	+	−	−	1
Sustained hypertension	−	−	+	−	−	−	−	1

The temperature was 101° F. and the pulse rate 86 per minute, and the respirations numbered 18 per minute. The rash was confined to the face and was of "butterfly" distribution. The cervical glands were enlarged and the fauces slightly inflamed. The apex beat was in the sixth intercostal space, two centimetres outside the mid-clavicular line. There was a blowing systolic murmur at the apex transmitted outwards to the left axilla. Both knee and ankle joints were swollen and reddened. The urine was normal.

There were mild anæmia (the hæmoglobin value being 11·5 grammes *per centum*) and leucopenia (3100 cells per cubic millimetre). L.E. cells were demonstrated repeatedly. Symptoms failed to respond to aspirin and to heavy doses of mepacrine, which was administered in doses of 100 milligrammes twice daily to a total dosage of three grammes. A partial remission was obtained with cortisone. After extraction of teeth on May 18, her condition deteriorated rapidly; stomatitis and gingivitis developed, and large hæmorrhagic blebs began to appear on the trunk, back and arms. Oliguria and anuria were shortly followed by death in uræmia.

Permission for autopsy was refused.

In this case disseminated *lupus erythematosus* presented with joint manifestations similar to those of acute rheumatic fever and progressed rapidly to death in uræmia within four months of the first symptoms. The fever and arthritis failed to respond to heavy salicylate dosage. Mepacrine was ineffective. Cortisone relieved the symptoms for only a short time. L.E. cells were observed in the peripheral blood during a therapeutically induced remission.

CASE III.—L.B., a housewife, aged thirty-eight years, with three children, was admitted to hospital on August 17, 1950. Eight months previously she had developed arthritis of all finger joints, which had persisted for two months, and about one month after the onset of the arthritis had noticed an irritating rash on the face, neck, chest, forearms and elbows. A fortnight before her admission to hospital the arthritis had recurred and the joints of the fingers and wrists had become painful and swollen. She felt extremely weak and tired.

The rash was maculo-erythematous in character and somewhat scaling. There was acute arthritis of the fingers, wrists and elbows. The temperature was 100° F., the pulse rate was 104 per minute, and the respirations numbered 24 per minute. The apex beat was in the sixth intercostal space outside the mid-clavicular line, and there was gallop rhythm with a systolic murmur. The blood pressure was 200 milli-

TABLE III
The Results of Laboratory Investigations

Findings	Case Number							Total
	I	II	III	IV	V	VI	VII	
Anæmia (less than 4,000,000 erythrocytes per cubic millimetre)	+	+	+	+	+	+	+	7
L.E. cells	+	+	+	+	+	+	+	7
X-ray abnormalities of chest	+	+	+	+	+	+	+	7
Leucopenia (less than 4000 leucocytes per cubic millimetre)	+	+	+	+	+	+	−	6
Albuminuria	−	−	+	+	+	+	+	5
Inversion of albumin-globulin ratio	•	•	+	+	+	+	+	5
Raised erythrocyte sedimentation	•	+	+	+	+	•	+	5
Raised blood urea nitrogen level	•	−	−	+	−	+	+	3
Thrombocytopenia	+	−	−	−	+	−	−	2
Result of gonococcal complement fixation test	•	•	•	•	•	+	•	1
Result of Wassermann test	•	−	•	−	−	−	−	0

• No test performed.

metres of mercury, systolic, and 120 millimetres, diastolic. The lungs were clinically clear. Neither liver nor spleen was palpable. The urine contained a trace of albumin, and the specific gravity was 1014. Occasional red cells and granular casts were seen in each high power field. Mild anæmia was present (the hæmoglobin value was 11·5 grammes *per centum*), with moderate leucopenia (3500 cells per cubic millimetre). L.E. cells were present in the peripheral blood.

She was given a course of penicillin without benefit; the temperature remained between 99° and 104° F. Congestive cardiac failure gradually supervened, and she died after a gradual deterioration of her condition on November 6.

Autopsy revealed pericardial, pleural, peritoneal and retroperitoneal serosal reaction, pleural and pericardial effusions, ascites, Libman-Sacks endocarditis involving the mitral valves and extending on to the wall of the left ventricle with superimposed bacterial vegetations, pulmonary œdema, and multiple scattered abscesses due to *Pseudomonas pyocyanea* in kidneys, spleen, brain and meninges.

The cause of death was congestive cardiac failure with terminal septicæmia.

In this case disseminated *lupus erythematosus* presented with rheumatoid type arthritis, rash and weakness. The duration of the illness was one year. Death occurred in congestive cardiac failure.

Rash

A rash was present at some time during the illness in all cases. In Case I a chronic discoid lupus rash had been present for twenty-five years and in Case IV for five months, and in Case II it was transient and somewhat atypical. In its fully developed state it involved the butterfly area of the face, the forehead, the backs of the ears, the front of the chest, the elbows and the fingers. The rash was maculo-erythematous at first and tended to scale early in its course, often leaving some residual pitting. There was a pronounced tendency for the pigmentation to persist after the rash had faded. In Case IV all these features were present, and in addition there was extension over the trunk and buttocks, which persisted for two years until her death. However, the evolution of the disease without the appearance of any cutaneous manifestation is well attested (Rakov and Taylor, 1942; Tumulty and Harvey, 1949; Griffith and Vural, 1951).

Pulmonary Involvement

The occurrence of pulmonary manifestations during the course of disseminated *lupus erythematosus* has been repeatedly emphasized. In all cases in the present series there were clinical signs suggestive of pulmonary disease. Intermittent chest pain was present in six cases, and in all of these there was pleural effusion at some time or other. In four cases pleural thickening was found on X-ray examination, and in Case V aspiration of fluid was made difficult by the thickened pleura. The pain was inconstant in distribution and character. It was sometimes pleuritic in type, but more often continual, dull and poorly localized. Most patients complained of chest pain when clinical and radiological signs of lung involvement were obvious, but there was a tendency for the pain to persist even during the remissions of the disease. The extensive pleural adhesions found at autopsy in three of the cases were evidence that pleural involvement could easily have accounted for the persistent chest pain. Dyspnœa was a common symptom and occurred early in the course of the disease. Its severity was not readily correlated with the clinical and radiological findings, and oxygen afforded little relief. Only one patient had pulmonary tuberculosis, and this was in an inactive, healed form. Terminal bronchopneumonia was common to all the subjects examined at autopsy.

Cardiac Involvement

Enlargement of the heart was present in six cases, and a systolic murmur in all. Five patients had a pericardial friction rub, which was always transient and unassociated with typical substernal pain. No correlation could be established between the cardiac signs and the presence of Libman-Sacks endocarditis. The myocarditis, anæmia and fever seem sufficient to produce a systolic cardiac bruit quite apart from any endocardial lesion, and undue emphasis should not be placed upon macroscopically evident structural changes in the valves. Despite the extensive cardiac damage, auricular fibrillation did not occur. Gallop rhythm was audible at some time in four cases. Hypertension was present in Case III and transitorily in Case IV, but was absent in Cases II and VI, despite the severe renal involvement. It was thought that the severity of the myocardial lesion precluded a significant rise in blood pressure. In the series of Shearn and Pirofsky (1952), hypertension occurred in 32% of cases.

Electrocardiograms were recorded in five cases. All showed sinus tachycardia. Four showed some type of abnormality; low voltage was present in all, and *T* wave inversion or depression in three. The *P-R* interval was slightly lengthened in Case V. The findings were non-specific, suggesting moderately severe to severe myocardial damage in those cases in which such damage was readily recognizable clinically, but not advancing the understanding of its extent or location.

Neurological Manifestations

Haserick and his co-workers (1951) have drawn attention to the frequency of epileptiform convulsions in disseminated *lupus erythematosus*, and state that *grand mal* seizures may precede the other signs of the disease by many years. They suggested that epilepsy accompanied by rheumatoid arthritis might constitute a prodromal symptom of *lupus erythematosus*. Case VI in their series resembles the following case, in that there was associated neurogenic vesical involvement.

CASE IV.—N.H., an unmarried comptometrist clerk, aged twenty-three years, was admitted to hospital on July 1, 1951. Ten weeks previously she had begun to experience general ill health, weakness and stiffness of the knees. A week later the glands behind her ears became swollen and sore, and a few days after this there appeared an irritating rash which involved the whole of her body, sparing only the face. This slowly faded after a few days, leaving mottled pigmentation on the buttocks, arms and legs. At this time she received a short course of a sulphonamide preparation. Six weeks before her admission to hospital she developed swelling of the ankles, wrists and fingers, a troublesome unproductive cough and intermittent fever. She experienced continual nausea, but no vomiting. Three days before her admission to hospital she developed acute retention of urine. There was no history of preceding illness, and the family history was non-contributory.

The patient on examination was an acutely ill young woman, flushed and disorientated, with sordes about the lips. The temperature was 101° F., the pulse rate was 100 per minute and regular, and the respirations numbered 24 per minute. The blood pressure was normal. A blotchy, pink, erythematous rash involved the whole of the trunk and limbs. The post-auricular glands were enlarged and tender, and generalized lymphadenopathy was present. Signs of consolidation were present at both lung bases, there was an apical systolic murmur, and both liver and spleen were palpable and tender. No ankle or knee jerks could be elicited.

The results of laboratory investigations were typical, and L.E. cells were demonstrated in the peripheral blood.

Symptoms decreased without treatment, the rash gradually faded and she was discharged from hospital after six weeks. The illness ran on for the next twenty months, during which period she was readmitted to hospital three times. Joint pains persisted, and dizzy turns lasting ten to fifteen minutes, diarrhœa, persistent albuminuria and choreiform movements of the hands were noted during this time. In November, 1951, she responded well to a course of ACTH, but subsequent courses had less effect, and she developed hallucinations and systematized delusions so that treatment was abandoned. Mepacrine given shortly after this produced no demonstrable improvement. In May she responded well to cortisone, and was allowed to go home, taking 25 milligrammes twice daily by mouth.

Suddenly, early in March, 1953, she had five epileptiform fits in the space of two hours and was admitted to hospital in deep coma. The blood pressure was 200 millimetres of mercury, systolic, and 120 millimetres, diastolic, shortly after the last convulsion but fell within a few hours to normal. The blood urea nitrogen content was 36 milligrammes *per centum*. It was considered that the convulsions were a reflection of the disease itself and not due to the cortisone, which was therefore continued. Consciousness was gradually regained, and no further fits occurred. She began to cough up small amounts of blood, the temperature rose slowly, and she died in acute respiratory distress ten days after her admission to hospital.

Autopsy revealed profound anæmia, a pericardial, pleural, peritoneal and retroperitoneal serosal reaction, left ventricular hypertrophy, Libman-Sacks endocarditis, bronchopneumonia, and pronounced cortical changes in both kidneys.

The cause of death was terminal bronchopneumonia.

The illness in this case commenced with vague arthritis and terminated in two years. Signs of neurological involvement were prominent at all stages, and included acute retention of urine, absence of knee and ankle jerks, dizziness, transient psychoses, athetoid movements of the hands and terminal convulsions.

Glaser (1952) has described the lesions in the central nervous system as widespread cerebral angiitis affecting mainly the vessels of the grey matter and leading to patchy encephalomalacia. Sensory loss was not detected in any of the present cases, nor apparently has it been mentioned in the literature. Convulsions were present in three of these cases. In Cases IV and VI they occurred during the course of cortisone therapy, but ceased spontaneously despite the continued administration of this drug. The following case presented as acute encephalitis, a type of onset which does not seem to have been previously reported.

CASE V.—V.K., a farm girl, aged seventeen years, was admitted to the Royal Adelaide Hospital on March 10, 1953. Three months previously she had suffered an acute febrile illness with generalized glandular swelling, which had been diagnosed without laboratory confirmation as infectious mononucleosis. Since that time she had not been well, complaining of weakness, nervousness, anorexia and some photophobia. Forty-eight hours before her admission to hospital she began to complain of increasing headache and neck stiffness, and the temperature rose to 103° F. Pain in the right shoulder commenced shortly afterwards, and she had some difficulty in swallowing. The menstrual history was normal. Some six years previously she had suffered an illness with flitting joint pains, which had been diagnosed as rheumatic fever.

She was admitted to hospital with the diagnosis of early bulbar poliomyelitis.

On examination, the girl was flushed and drowsy, with cracked and swollen lips and a dusky erythematous rash on the cheeks, the nose and the posterior auricular region. The temperature was 105° F., the pulse rate was 120 per minute, and the respirations numbered 24 per minute. Pronounced neck and back stiffness and Kernig's sign were present. Soft, moderately enlarged glands were palpable in the axillæ and groins. The left side of the palate moved less than the right, and there was generalized weakness of the limbs without actual paresis. The heart was not enlarged

on clinical examination, but there was a soft apical systolic bruit. The lungs were normal on clinical examination, and apart from slight generalized tenderness no abnormality was detected on abdominal palpation. There was equal slight weakness of the limb reflexes, but the remainder of the examination of the central nervous system gave normal findings.

The results of laboratory investigations were as follows. Lumbar puncture produced cerebro-spinal fluid under an initial pressure of 180 millimetres of water; there was a normal response to Queckenstedt's test. The fluid was clear and colourless; it contained 100 cells per cubic millimetre, of which 95% were lymphocytes and 5% polymorphonuclear cells. The protein content was 95 milligrammes *per centum*. The urine contained a trace of albumin, and an occasional red cell and hyaline cast. There were mild anæmia (hæmoglobin value 8·8 grammes *per centum*) and leucopenia (2200 leucocytes per cubic millimetre); L.E. cells were present and persisted until the patient's discharge from hospital. The serum protein content was high (7·5 grammes *per centum*), and the albumin-globulin ratio was inverted.

The temperature remained elevated for several days and then slowly resolved by lysis, although throughout the remainder of her stay in hospital an irregular evening pyrexia persisted, the temperature seldom rising above 100° F. By the third day the rash had appeared on the elbows and finger tips and begun to fade from the face, after which it gradually disappeared altogether. Apical gallop rhythm was audible and persisted for a week, to be replaced by a loud blowing systolic murmur. Troublesome pustular stomatitis developed, which did not respond to chemotherapy. Cortisone treatment was begun on March 29, and resulted in gradual improvement in the patient's clinical condition. Mepacrine, 100 milligrammes twice daily, was also given, but its effect could not be assessed in the presence of cortisone therapy. On this régime there was a gradual evolution of a "Cushingoid" appearance, and the patient was discharged from hospital taking cortisone by mouth. When last examined she was well, and L.E. cells could not be demonstrated in the peripheral blood.

In this case disseminated *lupus erythematosus* presented as diffuse encephalitis. The rheumatic fever and infectious mononucleosis diagnosed earlier may have been the first indications of the disease. There was slow improvement without initial specific therapy, and good clinical remission was obtained with optimal dosage of cortisone.

Stomatitis

Of the other clinical features noted in Tables I and II, the presence of severe stomatitis in six cases was noteworthy. In two it followed shortly after the onset of the rash, in the remainder, during the later stages of the illness. The lesions commenced as small papules on the inner aspects of the lips and cheeks and occasionally on the gums. In Case II similar lesions were present over the forearms and trunk.

LABORATORY FINDINGS

The laboratory findings are summarized in Table III. They show the anæmia and leucopenia which are outstanding characteristics of the disease (Conley, 1952; Michael *et alii*, 1951). It has been suggested that hypersplenism of the secondary or acquired type may be the cause of the peripheral blood changes, since the bone marrow is normal or hyperplastic (Dubois, 1952). The rapidity with which the anæmia developed in the absence of signs of hæmolysis was a striking feature. Acquired hæmolytic anæmia may be an initial manifestation of lupus, and any such case merits investigation for the phagocytic cell. Depressed serum protein levels were also a common occurrence, and the albumin-globulin ratio was inverted in five cases. The positive response to the gonococcal complement fixation test in Case VI is regarded as a further indication of the disturbed serum protein constituents. "False positive" Wassermann reactions occur in many cases (Rein and Konstant, 1950; Montgomery and McCreight, 1949).

DIAGNOSIS

In the absence of the typical cutaneous manifestations, disseminated *lupus erythematosus* should be suspected in any unusual conjunction of clinical features. Such conditions include epilepsy and rheumatoid arthritis, leucopenia and nephritis, pericarditis and pleurisy with effusion, Raynaud's phenomenon and hæmolytic anæmia or any combination of these conditions. The anæmia or epilepsy may precede the termination of the illness by many years, and although the association may possibly be fortuitous, increasing numbers of reported cases strengthen their claim to a common ætiology.

The following case demonstrates the association of long-standing anæmia.

CASE VI.—J.M., a housewife, aged twenty-three years, was admitted to hospital on January 16, 1953. She had been treated for anæmia by several practitioners for many years, but had always been tired and listless. However, she had been able to bear a normal infant eleven months before her admission to hospital. About six months after delivery she had noticed puffiness of the eyes and swelling of the ankles, which lasted for nearly three weeks. Five weeks before her admission to hospital she became increasingly dyspnœic, developed polyarthritis and noticed that her urine was darker than normal. The arthritis responded poorly to salicylates, and the œdema of the face and ankles recurred from time to time. Menstruation had been irregular since its commencement. Apart from the history of anæmia there had been no significant previous illness. Her father had died from kidney trouble.

The patient was a thin, pale, freckled young woman. The temperature was 100·6° F., the pulse rate was

104 per minute, and the respirations numbered 26 per minute. The blood pressure was normal. A soft systolic murmur was audible at the cardiac apex. Both liver and spleen were just palpable. Generalized mild lymphadenopathy was present, and over the legs and feet were scattered purpuric spots. The diagnosis on her admission to hospital was septicæmia.

The results of laboratory investigation were as follows. The hæmoglobin value was 9·4 grammes *per centum* (62%); the white blood cells numbered 3700 per cubic millimetre, and the differential count gave normal results. The urine contained "heavy" albumin, eight to ten leucocytes per high-power field, and a few coarsely granular casts. X-ray examination of the chest revealed gross enlargement of the heart, particularly of the right border. The blood urea nitrogen content was 33 milligrammes *per centum*. Repeated attempts at blood cultures and serum agglutination tests gave negative results. The gonococcal complement fixation test gave a strongly positive result.

During the next few days the temperature remained elevated, and the purpuric spots extended to cover the front of the chest and the inside of the mouth. By the end of the week severe ulcero-hæmorrhagic stomatitis had developed, which failed to respond to penicillin or terramycin. The blood urea nitrogen content had risen to 100 milligrammes *per centum*. About that time a pericardial friction rub was heard and persisted for four days. L.E. cells were then discovered in the peripheral blood. Despite cortisone therapy there was little improvement in her condition, and she died in uræmia on April 8.

Autopsy revealed a pericardial, pleural, peritoneal and retroperitoneal serosal reaction, with superimposed acute hæmorrhagic pericarditis, and multiple, firm, bluish-coloured, discrete pulmonary nodulations about one centimetre in diameter. The heart was hypertrophied without endocarditis. In both kidneys pronounced cortical changes were present.

The cause of death was uræmia.

In this case *lupus erythematosus* presented with arthritis, nephritis and long-standing anæmia. The clinical findings at first suggested septicæmia. A rash was present on the face only fleetingly, the skin manifestations being predominantly hæmorrhagic. Death occurred after nine months of serious illness, but the condition may have existed for many years before.

Demonstration of the typical L.E. cell clinches the diagnosis, although the absence of the phenomenon does not vitiate it, since the cell is found in only 80% of acute cases (Dubois, 1952). It tends to disappear during spontaneous and therapeutically induced remissions, and it has not been found as a rule in the chronic discoid form of the disease (Barnes *et alii*, 1950; Marten and Blackburn, 1953). The specificity of the phenomenon has been extensively investigated by these workers, who have failed to recover the typical cell from a large number of the so-called collagen diseases or from unrelated conditions. Hargraves reported finding the cell in one case of multiple myeloma, but Trubowitz (1950) suggests that this may have been a plasma cell containing amyloid material, a similar phenomenon having been observed in a case of his own. From time to time reports of "false positive" test results are reported (Lee *et alii*, 1951; Walshe and Zimmerman, 1953); but most of these patients will ultimately show other changes of disseminated *lupus erythematosus* (Dubois, 1953). Dubois, as a result of a three years' study on 700 L.E. preparations, states that the test, if the result is positive, is pathognomonic for the disease. A negative finding, as mentioned previously, has not the same significance. Haserick and Lewis (1950) have demonstrated that the formation of L.E. cells depends upon the presence of an abnormal factor in the γ globulin fraction of the plasma, and Haserick (1951) suggests that the cell may be absent if the serum globulin level is low.

Typically, the cell is a polymorphonuclear leucocyte which contains a deeply staining homogeneous inclusion body at the periphery. The nucleus of the cell may be crowded into the opposite corner of the cytoplasm and considerably distorted. Sometimes a ring of polymorphonuclear cells may be seen surrounding a fragment of this hæmatoxylin-staining material, which is lying free in the plasma. In all cases in this series the typical cell has been found either in the sternal marrow or in the peripheral blood. Earlier examinations were performed on heparinized blood; but a simpler and more effective method with the use of defibrinated blood without anticoagulant has recently been employed (Marten and Blackburn, 1953). In most cases the phenomenon was observed to occur in polymorphonuclear leucocytes; but in Case V an abnormal monocyte with an engulfed red cell was observed on two separate occasions during therapeutically induced remission of the disease.

PROGNOSIS

If such isolated symptoms as epilepsy and rheumatoid arthritis are to be accepted as the earliest manifestations of dissemination in *lupus erythematosus*, previous estimations of the prognosis become too short. In an extensive review of 44 of their own cases and 279 culled from the literature, Jessar *et alii* (1953) found that 22% of the patients remained alive for periods in excess of five years. Some 40% of untreated patients have spontaneous remissions (Dubois, 1952). In the present series, five patients died within periods varying from four months to two years, although two patients (Cases IV and V) may have had the disease for a much longer period. The presence of severe renal involvement with red blood cells and casts

in the urine and a rising blood urea nitrogen level would seem to be of poor prognostic significance, since cases showing these features in the early stages of the disease progressed rapidly to a fatal termination. There is as yet no evidence that any form of treatment prolongs the course of the disease, and the prognosis remains grave (Soffer and Bader, 1952).

TREATMENT

Cortisone and ACTH will induce remissions in *lupus erythematosus* for varying periods of time. They do not cure the condition, but the distressing symptoms disappear on adequate dosage and the patient is much more comfortable. Of the two drugs, cortisone seems preferable, being more certain in its action and effective on oral administration. Emphasis has been placed on adequate dosage, and Dubois (1952) states that the therapeutic ideal is rapidly to induce a " Cushing " state, with moon face, slight hirsutism and moderately raised blood pressure. The maintenance dose must be large enough to inhibit the symptoms of the disease. The necessity for a large initial dose of cortisone was well demonstrated in Cases IV and VII, in which smaller amounts failed completely to halt the course of the disease. Too rapid withdrawal of the drug will result in a severe exacerbation which is often most difficult to control. There is some evidence to suggest that the administration of cortisone and ACTH tends to reduce the frequency of natural remission of the disease.

The earliest sign of remission under treatment is a fall in temperature, and this may be used as a guide to the adequacy of dosage. Joint manifestations regress soon afterwards, but the pulmonary signs may take some time to clear, and residual radiological abnormalities commonly persist. Anæmia and raised sedimentation rate become corrected more slowly, the latter sometimes not at all. Renal abnormalities including hæmaturia, casts in the urine, albuminuria and a raised blood urea nitrogen level may or may not disappear during treatment; but their persistence is a bad sign. In Case II evidence of renal involvement appeared after the commencement of cortisone therapy and progressed despite increased dosage.

The use of cortisone and ACTH makes the interpretation of some of the important manifestations of the disease extremely difficult. Hypertension, convulsions, œdema and psychosis may be due to the disease itself or to the treatment. They were present in Case IV during the later stages of the illness, and disappeared despite the continuation of therapy. The absence of a raised blood pressure, the onset of clinical relapse and the presence of fever, all tend to suggest that these signs are due to the disease itself, and as such necessitate increased dosage of the hormonal preparation. Problems of this type were present in Case VII.

CASE VII.—G.R., an unmarried typist, thirty-one years of age, was admitted to hospital on June 11, 1952, with severe acute polyarthritis of seven days' duration. There had been no response to intensive salicylate therapy given prior to her admission to hospital.

The patient was a flushed, red-haired girl in considerable pain. All the large joints were involved in acute arthritis, effusions were present in both knee joints, and all movements were limited by extreme pain. Apart from a soft systolic murmur, the remainder of the examination revealed no abnormality. Slight anæmia was present (the hæmoglobin value was 11·9 grammes *per centum*) and there was a leucocytosis of 10,000 cells per cubic millimetre. The diagnosis was considered to be acute rheumatoid arthritis. Cortisone was given in the usual dosage, but there was no response until a much larger schedule was employed. With this there was a gradual improvement, and she was discharged from hospital.

She was readmitted to hospital three months later, suffering from bilateral pleurisy and a small effusion which had followed a cold with sore throat one week previously. Mild arthritis was present, having recurred one week after her discharge from hospital. Three attempts at aspiration of the effusion were unsuccessful, and at each attempt an abnormally thickened pleura could be felt to resist the needle. The temperature gradually fell and the pleurisy gradually resolved, and she was discharged to a convalescent home.

She was readmitted to hospital again on December 19, 1952, complaining of loss of appetite, abdominal pain and diarrhœa of three weeks' duration. She had had an afternoon rise of temperature for one week, and for the past three days she had noticed a rash on her face. The temperature was 102° F., the pulse rate was 132 per minute, and the respirations numbered 50 per minute. There was an erythematous maculo-papular eruption of " butterfly " distribution on the face, the backs of hands and the pad of the right index finger. The posterior occipital glands were enlarged and tender, the apical systolic murmur and arthritis were as before. The urine contained " heavy " albumin, 20 to 30 red blood cells per high-power field and three to six granular casts per high-power field. The blood urea nitrogen content was 42 milligrammes *per centum*.

On December 20, L.E. cells were found in the peripheral blood. She was given mepacrine without effect. Cortisone in a dosage of 50 milligrammes every six hours induced a therapeutic remission, but lowering of the dosage soon resulted in the return of symptoms and the appearance of a pericardial friction rub. The dosage was again increased to 50 milligrammes every six hours, and she remained relatively well until six days after the commencement of cortisone therapy, when she had two *grand mal* epileptiform convulsions. The blood pressure immediately after both of these was normal. No further seizures occurred despite the continued cortisone therapy. She later developed severe hæmorrhagic stomatitis, but the symptoms gradually subsided, and she was discharged from hospital taking cortisone by mouth, afebrile, but with the rash still present on her fingers

This girl presented with two episodes of acute generalized arthritis, which preceded the appearance of the typical rash. Convulsions occurred in the absence of hypertension or uræmia, and ceased despite the continuation of cortisone therapy. There was no response to low oral dosage of cortisone, but immediate improvement followed the use of large intramuscular doses. Salicylates and mepacrine were ineffective.

Mepacrine has been used successfully in the treatment of chronic discoid lupus for some time (Page, 1951). Page noted dramatic improvement in one case of acute disseminated lupus and relief of the arthritic symptoms in another case of chronic discoid lupus. The drug was administered to five patients in the present series, both before and during treatment with cortisone and ACTH. No benefit was evident when a dosage of 100 milligrammes twice daily was used, but the protracted courses of treatment which Page employed were not carried out. O'Leary *et alii* (1953) have recently emphasized the dangers of such long-term treatment, and consider that the use of the drug is unjustified in the presence of systemic manifestations.

The role of sulphonamides and penicillin in the treatment of disseminated *lupus erythematosus* has been much debated since some cases were reported in which the symptoms were definitely made worse by their administration (Propert, 1940; Gold, 1951). However, so great is the tendency to cutaneous and respiratory infection that some form of chemotherapeutic or antibiotic treatment becomes essential during the course of the illness. Aureomycin and chloramphenicol may further accentuate the troublesome stomatitis and proctitis, so that they must be used with some care. Sensitivity tests would seem to be indicated whenever possible.

Dubois (1952) has advocated the use of large doses of testosterone propionate in the treatment of the disease " in order to combat the catabolic effects of ACTH and cortisone, and possibly to inhibit the fundamental abnormality of *lupus erythematosus* ". He states that it is difficult to " virilize " patients in the active phase of the disease, but that this becomes possible during a clinical remission. No patients in this series received testosterone propionate.

Apart from the use of ACTH and cortisone, the treatment remains symptomatic, with the administration of a diet of low sodium content to those patients who are receiving these drugs or in whom there is evidence of cardiac failure. Attention must be paid to the most superficial infections, and the patient should avoid such exciting factors as exposure to sunlight.

PATHOLOGY

Four of the patients came to autopsy. The most striking macroscopically evident feature was the intensity of the serosal reaction. The pleura, pericardium, peritoneum and retroperitoneal tissues were all involved in a semi-fluid, gelatinous, adhesive thickening. This reaction was most intense in Cases III, IV and VI. In Case VI uræmic pericarditis was superimposed, and was obviously quite distinct from the underlying serosal reaction. The abdominal viscera were covered by thickened peritoneum, and the gall-bladder in all three of these subjects was represented by a thickened, white-walled cord. I have noted similar appearance of the gall-bladder in a case of *polyarteritis nodosa*, and in a case of malignant hypertension without discoverable acute vascular lesions in the gall-bladder wall.

The heart was enlarged in all cases, varying in weight from 300 to 450 grammes. There was universal adherent pericarditis of the type described in Cases IV and VI, with extension on to the adjacent pleura. Endocarditis was present in Cases III and IV and conformed to the description of Libman and Sacks (1924), except that in both cases it was confined to the mitral valve. The vegetations were nodular, firm and greyish-yellow, and extended from the valve surface on to the wall of the ventricle and the papillary muscle in Case IV. (See Figure I.) No indication from the clinical history or progress of the case could be found to predict the presence of this lesion, and the varying degrees of structural alteration seen on histologic examination in some apparently normal valves serve to emphasize the fact that the vegetations are only a further stage in this structural change. In Case III there were friable vegetations superimposed on the firm underlying endocarditis, and culture from these yielded a growth of *Pseudomonas pyocyanea*.

The lungs were bound to the chest wall in Cases III, IV and VI by easily-parted gelatinous adhesions. Patchy bronchopneumonia was common to all these cases, with overlying massive œdema in Case III. Throughout the parenchyma in Case VI there were scattered firm, bluish-coloured, discrete nodules about one centimetre in diameter. They were found to consist of areas of focal necrosis and intense polymorphonuclear infiltration. Apart from two calcified foci in Case I, there was no evidence of pulmonary tuberculosis.

The kidneys were larger than normal in all cases. They were intensely œdematous in Cases I, IV and VI, and bulged from the incised capsule, which peeled with ease, a pale, mottled surface with areas of dull red and yellow being left. Occasional subcapsular hæmorrhages were noted in these three cases. The cortex was remarkable in all specimens. In Case III the appearance was obscured by the presence of

FIGURE I

A verrucous vegetation on the papillary muscle of the posterior leaflet of the mitral valve. Smaller vegetations are seen on the valve itself. Case IV.

multiple abscesses, but in the remainder it was normal or larger than normal in size and obviously œdematous, and contained areas of extreme pallor alternating with congestion. The medullæ were œdematous and the vessels appeared normal.

The spleen was enlarged in Cases IV and VI, but apart from the adherent peritoneum there was no remarkable macroscopically evident change. Both of these patients had generalized lymphadenopathy.

Apart from the generalized congestion, there was no gross abnormality in the brain in Cases I and IV, but in Case III terminal generalized meningitis was present.

Histopathology

Varying degrees of the fibrinoid change in the collagen bundles were found in all cases, the heart and pericardium showing the most severe changes. For the most part the structural alteration was obvious, varying from diffuse, homogeneously stained areas of swelling in the interfascicular supporting tissue of the muscle bundles to larger sheets of coarsely fibrillated acellular material. (See Figure II.) There were also fine, clear, cleft-like areas between the muscle fibres, which on being stained with van Gieson's stain or toluidine blue were seen to be areas of swollen collagen tissue. Cellular infiltration was prominent, and the infiltrating cells consisted mainly of small mononuclear cells, cardiac monocytes and histiocytes, many of which had distorted and pyknotic nuclei. Hæmatoxylin-staining bodies were observed only in Cases IV and VI. They were present in the pericardium and scattered throughout the myocardium as structureless, deeply-staining particles of varying shapes and sizes. No typical Aschoff bodies were seen, but the focal cellular collections previously described were similar in some cases to those seen in fulminating rheumatic carditis.

Blood Vessels.—The genesis of the vascular lesion could be well traced in all cases. It varied from a fine subintimal swelling of collagen tissue (Figure III) to complete obliteration of the vascular lumen. Between these

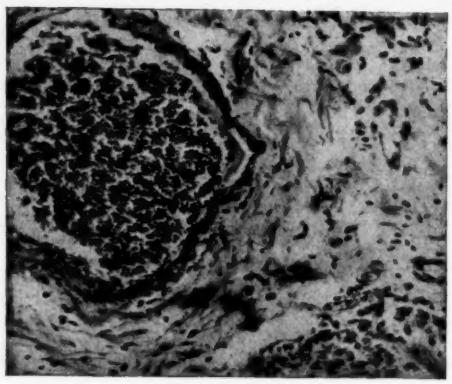

FIGURE II

An alveolar septum and pulmonary vein, showing the expansion and coarse fibrillation of the collagen bundles with infiltration by mononuclear cells, many of which are pyknotic. (×150; hæmatoxylin and eosin stain.)

two extremes could be traced a continuum of subintimal and subadventitial change, which was in places discrete and in others fused (Figure IV). Intimal proliferation over the swollen subintima was a common finding, and in several instances the occluded vessel appeared to have recanalized. These latter changes strongly resembled those first described as occurring in the vasculitis of rheumatic fever (von Glahn and Pappenheimer, 1926). In

Case VI a vessel seen in the papillary muscle or the heart was indistinguishable from vessels seen in cases of *polyarteritis nodosa*, although this was the only vessel of this type which was found. Another unusual vascular change was observed in the sections from this patient alone; the uterine, pericardial and gall-bladder vessels were deeply stained by hæmatoxylin in those areas where the fibrinoid degeneration was most pronounced (Figure V). The appearances closely resembled the uniform purple colour of the fragmented hæmatoxylin bodies found elsewhere in the same case, but subsequent staining for calcium by the method of von Kossa gave positive findings for these areas in the vessels and negative findings for the hæmatoxylin bodies in the kidneys, lymph glands and pericardium. This change does not appear to have been previously noted. Concentric periadventitial fibrosis of the splenic arterioles was pronounced in Cases III and IV, slight in Case I and absent in Case VI. There was

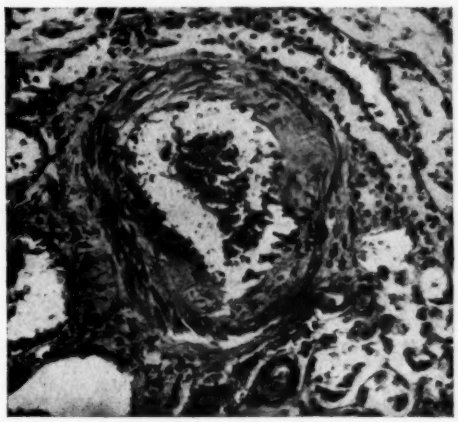

FIGURE III

A medium-sized renal vessel showing the earliest change of fine, subintimal, segmental swelling. (×180; hæmatoxylin and eosin stain.)

therefore no correlation between these changes and the presence of splenomegaly in this series (Figure VI).

The hæmatoxylin-staining bodies found in Cases IV and VI were present in the kidneys, cardiac valvular leaflets, myocardium, lymph glands and spleen.

Kidneys.—In the kidneys no fully formed "wire loop" lesions were seen, although some localized hyalinization of the capillary basement membrane was present in Cases II and IV (Figure VII). The commonest pathological change was a patchy focal thickening of the glomerular loops with adherence to Bowman's capsule (Figure VII). Occasionally this thickening had progressed to necrosis. In Case IV there were some hyaline thickening of the capillary basement membrane and a moderate degree of periglomerular fibrosis. In addition, many glomeruli showed segmental proliferation of the epithelium of Bowman's

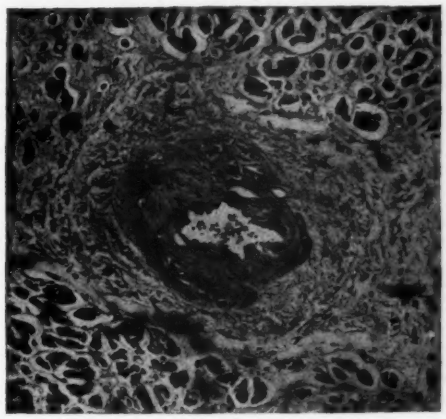

FIGURE IV

A more advanced vascular lesion in the myocardium with fusion of the subintimal and adventitial collagen changes. (×150; hæmatoxylin and eosin stain.)

capsule with the formation of epithelial crescents. The appearances were not typical of either type I or type II nephritis as described by Ellis (1942), but rather a combination of the early lesions of both types. In Case VI the appearances closely resembled those of acute nephritis with considerable proliferation of the glomerular epithelium. The kidneys in Cases I and II were not remarkable, except that those in the latter contained many abscesses. Arterial lesions similar to those already described were present in some degree in all cases, and were more pronounced in the larger arcuate and interlobular arteries. In this series only one patient (Case III) showed any severe degree of hypertension before death, and in none of the subjects was microscopic evidence of hypertensive vascular disease found. The hæmatoxylin-staining bodies found in Case VI were present in the lumina of the glomerular capillaries, in the interstitial tissue, and in the walls of the interlobular arteries. There was no true correlation between the degree of clinical renal impairment and the extent of the renal parenchymal damage.

Lungs.—The lungs showed a great variety of changes. In the pleura and alveolar septa were found varying degrees of fibrinoid alteration of their connective tissue matrix, which

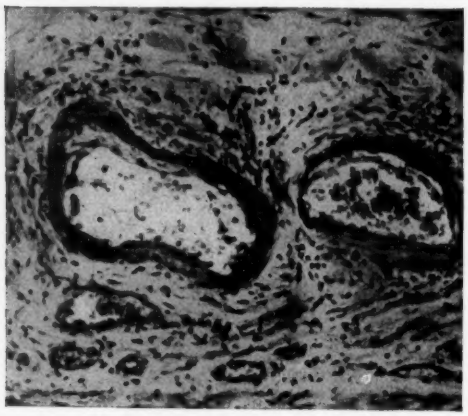

FIGURE V

Two pericardial vessels with subintimal swelling which is undergoing calcification. Note the cellular infiltration. (×400; hæmatoxylin and eosin stain.)

appeared coarsely fibrillated and infiltrated with normal and pyknotic monocytic cells (Figure II). Some of the alveoli were filled with fibrin;

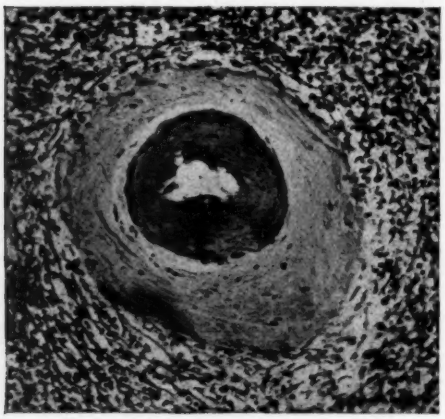

FIGURE VI

Periadventitial fibrosis of a splenic arteriole. (×400.)

others contained an exudate rich in polymorphonuclear cells, which extended into the surrounding lung parenchyma and were responsible in Case VI for the bluish nodules noted at autopsy. In these areas, necrosis of cells and lung tissue was particularly obvious. The changes were patchy in distribution and were not observed in the lungs in Case I, which showed pulmonary œdema and mild bronchopneumonia. Lesions of the blood vessels similar to those described above were seen in Cases I, III and VI. Overlying bronchopneumonia of varying degree was observed in all cases.

Brain.—The brain was available for study in only three cases. Apart from generalized vascular congestion there was no significant abnormality, and the focal encephalomalacia described by Glaser (1952) could not be seen. Such lesions would have been suspected clinically in Case IV from the very obvious involvement of the central nervous system.

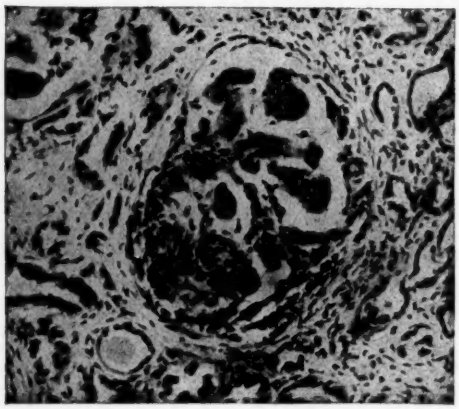

FIGURE VII

Patchy focal thickening of a glomerular loop with adherence to Bowman's capsule. A fine epithelial crescent is forming and the remaining glomerular capillary shows hyalinization. (×225; hæmatoxylin and eosin stain.)

CONCLUSIONS

Any attempt to correlate the clinical and pathological findings in such a prolonged disease as this must take into account several factors. The symptoms at onset may reflect only a local reaction of the disease, whilst the fully developed and terminal pathological appearance may have occurred only within the last few weeks. For this reason, the discussion of the frequency of Libman-Sacks endocarditis, of wire loop lesions in the kidneys and of the focal allergic reactions in the lungs seems unlikely to yield fruitful results. Again, it is now known that cortisone and ACTH may

materially alter the appearances of the tissues both in the normal animal and in patients suffering from varying allergic disorders. Baggenstoss *et alii* (1950) have described the appearances of the fibrosed and obliterated vessels, devoid of inflammation, in two cases of *polyarteritis nodosa* treated with cortisone, and lesions in the kidney identical with those observed in the intercapillary glomerulosclerosis of the human diabetic have been produced in animals by long-continued dosage with cortisone (Rich *et alii*, 1950; Rich, 1952).

It is thus extremely difficult to make any definite correlation between the clinical and pathological findings, and this difficulty is increased by the small number of cases in this series. Cardiac, renal, pulmonary and neurological symptoms are undoubtedly due to the profound alteration of collagen in the vessels and in the parenchyma; but the extent of this alteration has been surprisingly inconstant in its distribution and in its relationship to the major clinical features in individual cases. Yet this disparity is understandable when the widespread effects of failure of one important organ such as the heart or kidney is taken into account. No relationship between the pathological appearances of the heart and the presence of cardiac murmurs, blood pressure recordings or electrocardiograms has been established. No link between the severity of the renal lesion and the presence of clinical renal failure has been found. These findings concur with those of larger series in which clinico-pathological correlation was attempted (Montgomery and McCreight, 1949; Griffiths and Vural, 1950). Further investigation into the profound histochemical alterations which are already becoming apparent may show that the severity of the clinical picture depends on some unknown generalized body insult.

SUMMARY

Seven cases of disseminated *lupus erythematosus* at the Royal Adelaide Hospital in the last three years have been reported. The series includes an unusual case which presented as diffuse encephalitis with muscular weakness, neck stiffness and a pleomorphic cellular reaction in the cerebro-spinal fluid. The remainder of the cases serve to illustrate the bizarre and seemingly unrelated prodromal manifestations of the disease.

The pathological findings in the four patients who came to autopsy have been described. No definite correlation with clinical features could be made, and it is concluded that the varying degrees of structural change in this disease are not closely related to the severity of the clinical features. In the pericardial, uterine and gall-bladder vessels of one subject, uniform subintimal calcification was observed, and this change does not seem to have been reported before.

Cortisone proved the most useful drug in inducing a therapeutic remission; but three of the patients died during its administration. The difficulties of differentiating between the symptoms and signs of the disease itself and those produced by hormonal therapy have been stressed.

Mepacrine was used in five cases without benefit.

Three of the patients who presented with primarily arthritic manifestations were not relieved by heavy dosage of salicylates, and it is suggested that this failure in improvement may indicate the arthropathy of *lupus erythematosus*.

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ORDINARY MEETING, 1953

The Ordinary Meeting of the College in 1953 was held at Sydney from October 14 to 16. It was attended by 65 Fellows and 79 Members representative of all the Australian States and of New Zealand. Sir Charles Symonds of London, the Sims Commonwealth Travelling Professor for 1953, was present at the meeting. The President, Dr. Alex Murphy, was in the chair.

Scientific Sessions

W. E. George (New South Wales) opened the first scientific session with a paper entitled " A Series of Whole Lung Sections according to the Gough Technique and Illustrating the Development of Emphysema in Lungs of Coal Workers in New South Wales ".

R. A. Joske (Victoria) presented a paper entitled " Aspiration Biopsy of the Kidney, with Special Reference to Diabetic Renal Disease ".

E. G. Sayers (New Zealand) delivered a paper on " Chronic Hypopotassæmia ".

Sir Charles Symonds (London) delivered the G. E. Rennie Memorial Lecture entitled " Occlusion of the Internal Carotid Artery ".

F. R. Magarey (New South Wales) presented a paper entitled " Experimental Pulmonary Hæmosiderosis ", in which he described the similarity of both radiological and histological pictures in pulmonary hæmosiderosis and certain forms of coal-workers' pneumonokoniosis. Experiments were described in which hæmosiderosis was induced in rats by repeated endotracheal injections of blood. Discrete aggregations of hæmosiderin-containing phagocytes developed and persisted. These aggregations closely resembled those seen in human pulmonary hæmosiderosis in cases of long-standing pulmonary congestion, especially that associated with mitral stenosis. The conclusion was drawn that in the human disease these aggregations could result from diffuse intrapulmonary hæmorrhage, and were not necessarily a manifestation of small hæmorrhages from any particular anatomical site.

Russell Chisholm (New Zealand) opened the second scientific session with a paper on " The Treatment of Hypertension ".

W. B. Macdonald (Victoria) delivered a paper on " The Use of Cation Exchange Resins in the Management of Anuria in Childhood ".

C. R. B. Blackburn (New South Wales) presented, on behalf of the Clinical Research Unit of the Royal Prince Alfred Hospital, a paper entitled " Refractory Rickets due to Resistance to Vitamin *D* : Metabolic Balance Studies of Two Children ", in which two children, aged four and five years, with vitamin *D*-resistant rickets, were studied. Both had normal calcium, low phosphorus and high alkaline phosphatase levels in their sera. Their serum sodium, potassium, chloride and bicarbonate levels were normal. Metabolic balance studies revealed that there was decreased intestinal absorption of calcium, but this could be increased by the administration of massive doses of dihydrotachysterol (AT10). They were both resistant to relatively large doses of vitamin *D* by mouth or by intramuscular injection. Increased clearance of phosphorus in the urine of these children was attributed to secondary hyperparathyroidism, as appeared to be the case in most patients with osteomalacia from any cause. The abnormality responsible for the rickets was considered to be a low serum calcium level resulting from decreased intestinal absorption.

J. L. Allsop (New South Wales) delivered a paper entitled " Thallium Poisoning ". This paper was published in Australasian Annals of Medicine (1953), 2 : 144.

R. H. Vines and Lorimer Dods (New South Wales) presented a paper on " Female Pseudohermaphroditism. Response to Cortisone Therapy " (see page 5).

Clinical Meetings

Clinical meetings were held at St. Vincent's Hospital and at Sydney Hospital. The following demonstrations were given : " Ocular Myopathy ", K. B. Noad ; " Olivo-ponto-cerebellar atrophy ", George Selby ; " Nephritis and Pneumonitis Complicating Rheumatic Fever ", Ralph Reader ; " Torulosis ", W. L. Calov ; " Miliary Tuberculosis and Cerebral Tuberculoma ", M. R. Joseph ; " General Paralysis of the Insane ", W. J. G. Burke ; " Ventricular Tachycardia Treated with Procaine Amide ", Justin Markell ; " Nodular Panniculitis ", R. D. Puflett ; " Chronic Idiopathic Hypoparathyroidism ", J. H. Deakin ; " Staphylococcal Pneumonia with Multiple Lung Abscesses ", B. A. Curtin.

Office-Bearers

The following office-bearers were elected by the Council for the period 1954–1956 and will take office at the time of the Annual Meeting in 1954 :

President : C. G. McDonald.

Vice-Presidents : Ralph Whishaw, A. D. S. Whyte (New Zealand), Ian J. Wood.

Censor-in-Chief : T. M. Greenaway.

Honorary Secretary : H. Maynard Rennie.

Honorary Treasurer : W. P. MacCallum.

MEMBERSHIP

Admission of Members. An examination for Membership was held in Australia in September and October, 1953. The following successful candidates were admitted to Membership by the President at the Council meeting on October 14: John Benecke, R. B. Blacket, W. H. Cary, D. L. Hobson, J. G. Richards and Lyal Watson of New South Wales; J. W. Bennett, G. W. Cooper and P. M. Robertson of Victoria; G. L. Bennett of South Australia; R. F. O'Shea of Queensland; K. S. Millingen and N. M. Newman of Tasmania.

Obituary. The Council records with regret the death of the following Fellows of the College: Harold J. Ritchie of Sydney, President from 1944 to 1946; Sir Edmund Britten Jones of Adelaide; J. H. Young of Perth; and F. J. Watson of New Zealand.

Membership Roll. The College now has a roll of 287 Fellows and 414 Members.

GENERAL

Sims Commonwealth Travelling Professor. Sir Charles Symonds, Honorary Physician at the National Hospital, Queen's Square, London, visited Australia and New Zealand as Sims Commonwealth Travelling Professor in October and November, 1953. Sir Charles Symonds gave lectures and clinical demonstrations in Sydney, Melbourne and Adelaide during his visit to Australia, and in New Zealand he undertook similar work in Dunedin, Christchurch and Wellington, briefly visiting Auckland before his departure.

Scholarships. The Travelling Scholarship in Medicine for 1954 was awarded to J. L. Allsop of Sydney. The Joseph Thornton Tweddle Research Scholarship for 1953 was awarded to W. C. Boake.

Research Activities. Upon the recommendation of the Research Advisory Committee the Council has made grants to Dr. M. H. Cass to aid his work at the Royal North Shore Hospital, Sydney, on the metabolism and excretion of bilirubin in normal and in jaundiced patients, and to Dr. Jean Isbister to assist her work on staphylococcal infection in the newborn and the physiology of the draught reflex and its relation to gastro-intestinal symptoms in the baby.

Quarterly Publication of Australasian Annals of Medicine. At its meeting on October 14, 1953, Council decided that from 1954 AUSTRALASIAN ANNALS OF MEDICINE would be published quarterly, in February, May, August and November.

Representatives of the College. The following were appointed to represent the College: on the Board of Directors of Prince Henry Hospital, Sydney, R. Jeremy; on the Consultative Council for the Physically Handicapped, New South Wales, S. E. L. Stening; on the Wellington Hospital Appointments Committee, J. R. Boyd; on the Auckland Hospital Board Appointments Committee, E. J. Cronin; on the North Canterbury Hospital Board Appointments Committee, J. F. Landreth; on the Medical and Scientific Committee of the Anti-Cancer Council of Victoria, L. E. Hurley.

Future Meetings of the College. The Annual Meeting of the College in 1954 will be held in Melbourne, from May 26 to 29. The Ordinary Meeting will be held in Sydney, from October 13 to 16, 1954.

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